



## Kinetic Analysis of the Thermal Decomposition of Efavirenz and Compatibility Studies with Selected Excipients

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**SUMMARY.** In the present work, the thermal decomposition of efavirenz (non-nucleoside reverse transcriptase inhibitor with a prolonged half-life) was studied using differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG). Non-isothermal method was employed to determine kinetic data of decomposition process. The physical chemical properties and compatibilities of several commonly used pharmaceutical excipients (Methocel®K100, magnesium stearate, crospovidone, croscarmellose, microcrystalline cellulose 101) with efavirenz (EFZ) were evaluated using thermoanalytical methods. The thermal kinetic TG analysis under nitrogen atmosphere was studied at the heating rate of 5, 7.5, 10, 15 and 20 °C.min<sup>-1</sup>. The activation energy (*E<sub>a</sub>*) and the pre-exponential factor (log *Z*) were obtained by means Flynn-Ozawa-Wall (FWO) and Ozawa methods. Comparison of the thermoanalytical profiles of the mixtures with individual compounds did not give any evidence of interactions. For non-isothermal method the activation energy (conversion 10%) obtained are 99.62 kJ/mol and 88.34 KJ/mol by thermobalance model TA Instruments Thermal Analysis and TGA-50 Shimadzu, respectively.

**RESUMEN.** “Análisis Cinético de la Descomposición Térmica del Efavirenz y Estudios de Compatibilidad con Excipientes Seleccionados”. En el presente trabajo se estudió la descomposición térmica del efavirenz (EFZ), un no-nucleótido que es inhibidor de la transcriptasa reversa de prolongada vida media, utilizando calorimetría diferencial de barrido (DSC) y termogravimetría/termogravimetría derivada (TG/DTG). Se empleó el método no isotérmico para determinar los datos cinéticos del proceso de descomposición. Las propiedades fisicoquímicas y la compatibilidad de varios excipientes comúnmente utilizados con EFZ (Methocel®K100, estearato de magnesio, crospovidona, croscarmelosa, celulosa microcristalina 101) fueron evaluados utilizando métodos termoanalíticos. El análisis de la cinética térmica TG bajo atmósfera de nitrógeno fue estudiado a la velocidad de calentamiento de 5, 7.5, 10, 15 y 20 °C.min<sup>-1</sup>. La energía de activación (*E<sub>a</sub>*) y el factor pre-exponencial (log *Z*) fueron obtenidos por medio de los métodos de Flynn-Ozawa-Wall (FWO) and Ozawa. La comparación de los perfiles termoanalíticos de las mezclas con los componentes individuales no dio ninguna evidencia de interacciones. Para el método no-isotérmico la energía de activación (conversión 10%) obtenida fue de 99,62 kJ/mol y 88,34 KJ/mol utilizando termobalanzas modelo TA Instruments Thermal Analysis y TGA-50 Shimadzu, respectivamente.

### INTRODUCTION

Thermal analysis is a term used to describe the analytical techniques that measure the physical and chemical properties of a sample as a function of temperature or time <sup>1</sup>. The importance of thermal analysis methods has been emphasized by Waterman & Adami <sup>2</sup> in their review of methods of rapidly and accurately assessing the chemical stability of pharmaceutical dosage forms <sup>3</sup>. Thermal analysis is a routine

method for analysis of drugs and substances of pharmaceutical interest <sup>4-5</sup>.

Thermogravimetry (TG), in which the change in mass of a sample heated at constant rate is recorded and plotted vs. temperature, is an effective method of studying thermal stability and for determining the kinetic parameters of the decomposition of drugs and medicines <sup>6-8</sup>. It can be used in the quality control of drugs, with a view to improvement of final product and for

**KEY WORDS:** Efavirenz, Kinetics studies, Solid state interactions, Thermal analysis.

**PALABRAS CLAVE:** Análisis térmico, Efavirenz, Estudios cinéticos, Interacciones en estado sólido.

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determination of drug quality via technological parameters <sup>9</sup>.

Kinetic parameters such as activation energies and pre-exponential factors are calculated using integral and differential methods reported in the literature <sup>9</sup>. With experimental procedures, information about the kinetics of decomposition and in-use lifetime projections can be obtained. The ability to predict the lifetime is valuable, because the costs of pre-mature failure in actual end use can be high. TG provides a method for accelerating the lifetime testing of polymers so that short-term experiments can be used to predict the lifetime. The lifetime is considered when 10% mass loss is reached from a dynamic thermogravimetric analysis <sup>10</sup>.

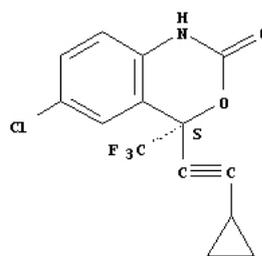
The fact that the temperature is altered in the thermal analysis means that special considerations must be given to thermodynamic and kinetic factors <sup>6</sup>. In kinetics, the emphasis is on the reaction rate. In TG, the substance mass as a function of time and temperature is used to assess the thermal stability and degradation of drugs, which includes the generation of kinetic data such as activation energies. One main purpose of kinetic analysis of solid decomposition is to determine Arrhenius parameters (activation energy, pre-exponential factor and reaction extent function) <sup>11</sup>. There are two ways to do this, using either isothermal or non-isothermal kinetic analysis <sup>12</sup>.

Incompatibility between drugs and excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy <sup>13</sup>. Study of drug-excipient compatibility is an important process in the development of a stable solid dosage form <sup>14</sup>. Drug-excipient compatibility testing at an early stage helps in the selection of excipients that increases the probability of developing a stable dosage form. As a result, energy associated with various thermal events (e.g., melting, glass transition temperature, crystallization, etc.) can be evaluated. This method has been extensively reported in the literature for testing compatibility of excipients with number of drugs. Use of DSC has been proposed as a rapid method for evaluating the physical-chemical interaction between two components. However, caution need to be exercised in the interpretation of DSC results <sup>13,14</sup>.

Thermoanalytical techniques are widely applied alone or as combined with microscopy, spectroscopy (UV, IR), X-ray powder diffractometry and mass spectrometry. During preformulation (tablet making, capsules, powders, etc.)

and for characterization of drugs. Thermoanalytical techniques are also used for incompatibility studies between drug(s) and excipient(s) upon preformulation. Incompatibility can lead to the loss of biological activity of drugs, complex formation, acid-base interactions and formation of eutectic mixtures <sup>15</sup>.

The objective of the present study was to evaluate the thermal behavior, compatibility with excipients and the kinetic analysis under non-isothermal (dynamic) conditions of EFZ. This drug is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with a prolonged half-life <sup>16</sup>. The EFZ was approved by the US FDA in September 1998 (Fig. 1). NNRTIs are highly potent antiretroviral agents that can be combined with nucleosides and/or PIs without added toxicity. NNRTIs should always be used in combination with other antiretrovirals to insure suppression of viral replication <sup>17</sup>.



**Figure 1.** Molecular structure of the efavirenz (EFZ).

## MATERIAL AND METHODS

### Materials

Efavirenz, C<sub>14</sub>H<sub>9</sub>ClF<sub>3</sub>NO<sub>2</sub> (8-chloro-5-(2-cyclopropylethynyl)-5-(trifluoromethyl)-4-oxa-2-azabicyclo[4.4.0]deca-7,9,11-trien-3-one), was obtained from Hetero Labs®. Excipients tested were: Methocel®K100, magnesium stearate (Dyne), crospovidone, croscarmellose, microcrystalline cellulose 101.

### Thermal behavior and compatibility studies

The mixed samples consisted of equal weights of EFZ and each excipient was individually weighed into amber glass vials to give composite weights of 20 mg. The binary mixtures was gently prepared at a 1:1 (EFZ:excipient) weight ratio by simple mixing with a spatula for 10 min.

DSC curves were obtained in a DSC-50 cell (Shimadzu) using aluminium crucibles with about 2 mg of samples, under dynamic nitrogen atmosphere (50 mL·min<sup>-1</sup>) and heating rate of 10 °C·min<sup>-1</sup> in the temperature range from 25 to 600 °C. The DSC cell was calibrated with indium

(*m.p.* 156.6 °C;  $\Delta H_{fus.} = 28.54 \text{ J.g}^{-1}$ ) and zinc (*m.p.* 419.6 °C). TG/DTG curves were obtained with a thermobalance model TGA 50 (Shimadzu) in the temperature range 25-900 °C, using platinum crucibles with ~3 mg of samples, under dynamic nitrogen atmosphere (50 mL·min<sup>-1</sup>) and heating rate of 10 °C·min<sup>-1</sup>.

### Kinetic investigation

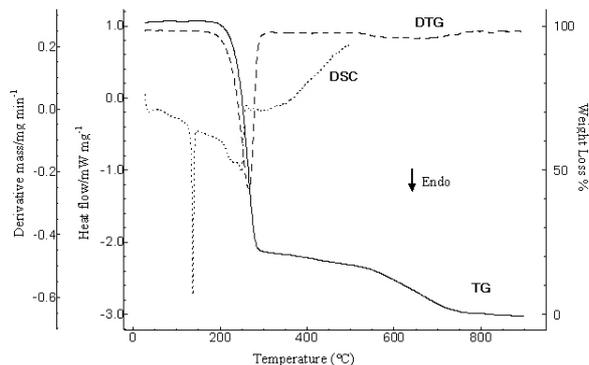
TG curves for kinetic investigation were obtained with a thermobalance model TA Instruments Thermal Analysis and TGA-50 Shimadzu. Non-isothermal kinetic investigation of EFZ degradation was obtained from TG data by application of Flynn-Wall-Ozawa (TA Instruments Thermal Analysis) and Ozawa method (Shimadzu) in which plot slope of log heating rate vs. 1000/T gives activation energy of process. In dynamic experiments were used heating rates 5, 7.5, 10, 15 and 20 °C·min<sup>-1</sup>, temperature range between 25-700 °C, using aluminum crucibles with ~5 mg of samples and under dynamic nitrogen atmosphere (100 mL·min<sup>-1</sup>). TG system was calibrated using a CaC<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O standard substance in conformity to ASTM standard<sup>18</sup>.

## RESULTS AND DISCUSSION

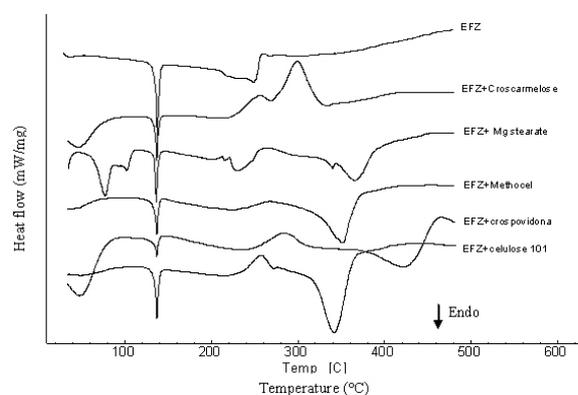
### Thermal analysis of EFZ and compatibility studies

DSC curve of EFZ (Fig. 2) shows a sharp endothermic peak that corresponds to melting in the range of 126 to 145 °C [enthalpy change ( $\Delta m$ ) = 49 J·g<sup>-1</sup>]. After melting, two peaks are observed due to thermal decomposition. The first indicates an endothermic event in the range of 180 to 260 °C presenting an enthalpy value of 143 J·g<sup>-1</sup> following an exothermic event characteristic of carbonization process. The TG/DTG curves (Fig. 2) indicate that the thermal decomposition process of EFZ occurs in two stages in the following temperature range and weight loss: 200-285 °C ( $\Delta m = 80\%$ ) and carbonization initiating at about 285 °C ( $\Delta m = 20\%$ ).

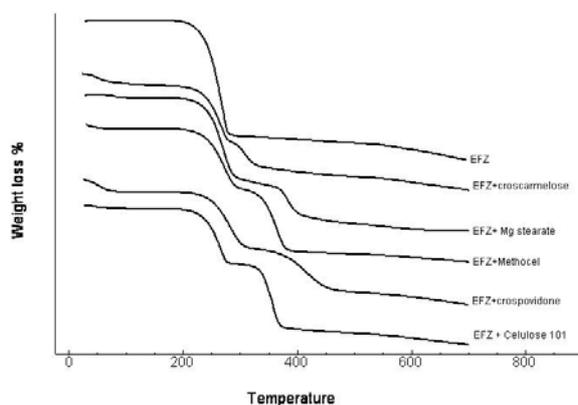
The thermal behavior of the binary mixture of EFZ and excipients (Fig. 3) shows the endotherm and exotherm characteristic of drug, indicating the presumable absence of incompatibility. Fig. 4 present the TG/DTG curves of the EFZ and binary mixtures. The temperature onset of thermal decomposition of EFZ is indicated in this figure for to compare the initial values of the excipients. The values of the melting peak temperature, fusion enthalpy, and temperature range of thermal decomposition and weight losses (%) of EFZ after mixing with excipients are listed in Table 1.



**Figure 2.** DSC and TG/DTG curves of EFZ obtained in dynamic nitrogen atmosphere (50 mL·min<sup>-1</sup>) and rate heating 10 °C·min<sup>-1</sup>.



**Figure 3.** DSC curves of EFZ and binary mixtures with excipients obtained in dynamic nitrogen atmosphere (50 mL·min<sup>-1</sup>) and rate heating 10 °C·min<sup>-1</sup>.



**Figure 4.** TG curves of EFZ and binary mixtures with excipients obtained in dynamic nitrogen atmosphere (50 mL·min<sup>-1</sup>) and rate heating 10 °C·min<sup>-1</sup>.

### Kinetic studies of thermal decomposition of EFZ

#### Non-isothermal method

Ozawa method, which is essentially the same as that of Flynn and Wall, represents a simple method to determine activation energies from TG curves. The activation energy calculated by using this method is called apparent acti-

Sample	Tonset melting DSC (°C)	Enthalpy of fusion (J·g <sup>-1</sup> )	Tonset dec. TG (°C)	Tpeak dec. DTG (°C)	Mass loss (%)
Drug					
EFZ	131.7	49.4	221.4	268.8	80.1
Drug/excipients					
Croscarmellose	131.8	23.0	233.5	265.9	38.3
Mg stearate	132.2	19.6	231.9	271.1	54.4
Methocel	131.7	16.1	232.2	270.4	39.5
Crospovidone	134.0	10.2	239.1	282.1	38.6
Cellulose 101	132.2	23.8	228.1	265.1	37.7

**Table 1.** Peak temperature and enthalpy values of EFZ and binary mixtures with excipients.

vation energy because it is the sum value of activation energies of chemical reactions and physical processes in thermal degradation<sup>18,19</sup>.

In order to determine the kinetic parameters of the first degradation step of the blends, the isoconversional method after Flynn, Wall and Ozawa (F-W-O) was applied. The method was derived from the basic kinetic equations for heterogeneous chemical reactions and therefore has a wide application, as it is not necessary to know the reaction order or the conversional function  $g(\alpha)$  to determine the kinetic parameters. F-W-O method is shown by the equation [Eq. 1]<sup>20</sup>:

$$\log g(\alpha) = \log (A Ea/R) - \log q - 2.315 - 0.4567 Ea/RT \quad [\text{Eq. 1}]$$

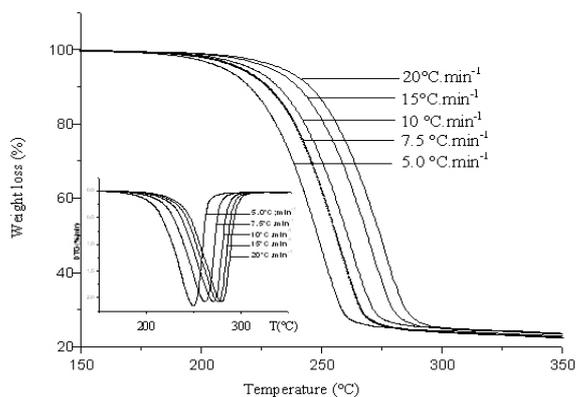
where:  $g(\alpha)$ -conversion functional relationship;  $A$ - preexponential factor;  $Ea$ - apparent activation energy;  $R$ - general gas constant;  $q$ - heating rate;  $T$ - absolute temperature.

For different heating rates at constant degree of conversion ( $\alpha$ ) [Eq. 2] is:

$$\log q = -0.4567 Ea/RT \quad [\text{Eq. 2}]$$

The degree of conversion is defined  $\alpha = (m_0 - m)/(m_0 - m_f)$ , where  $m_0$ ,  $m$ ,  $m_f$  refer to the initial, actual and final mass of the sample. Apparent activation energy is calculated from the slope of adjust straight line obtained by drawing the dependence  $\log q$  vs.  $1/T$  and the pre-exponential factor from the intercept of the straight line on the  $y$  axis<sup>20</sup>.

FWO methods are applied to calculate the dependence of  $E$  on  $\alpha$  (fractional mass loss), and the calculated values of the apparent activation energy at different extent of conversion<sup>21</sup>. Fig. 5 shows the TG curves obtained in the TA instrument of EFZ under nitrogen atmosphere at the heating rate of 5, 7.5, 10, 15, 20 °C·min<sup>-1</sup>. The TG signals indicate that the mass loss between 180 and 300 °C was completed in one



**Figure 5.** Weight loss (TG %) curves of EFZ at different heating rates  $\beta$  (5.0-7.5-10.0-15.0-20.0 °C·min<sup>-1</sup>) using TA instrument.

step. The DTG curves at the heating rate of 5, 7.5, 10, 15, 20 °C·min<sup>-1</sup> are depicted in inset Fig. 5. The DTG curves show the peak maxima at 248, 260, 269, 275 and 276 °C, respectively. The ASTM E698, Flynn-Wall-Ozawa (FWO) methods can calculate the obtained activation energy and  $\log Z$  of the decomposition process under non-isothermal conditions. The activation energies and  $\log Z$  (conversion 10%) obtained are 99.62 kJ/mol and 11.02 min<sup>-1</sup>, respectively.

A variation in activation energy can be observed for both elementary and complex reactions. An elementary reaction can show variable activation energy during its progress, as a result of product formation and the consequent heterogeneous nature of the residual solid sample. Such changes lead to systematic changes in the reaction kinetics. Solid-state reactivity of an elementary reaction could also be affected by experimental variables that can change at a reaction interface. Firstly, the isoconversional Ozawa method was used to calculate the activation energy for different conversion values by fitting the plots of  $\log b$  versus  $1/T$ <sup>22</sup>. The apparent activation energy was obtained employing the expression:

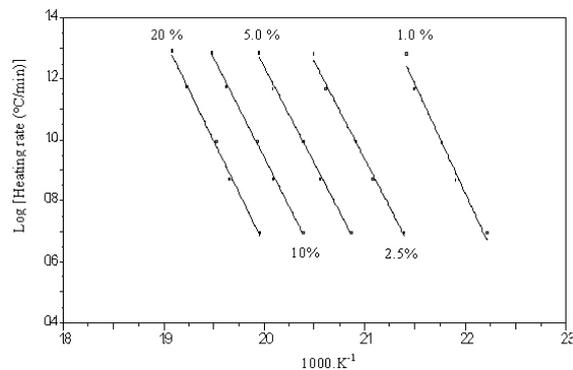
$$E \cong -4.35 \frac{\partial \log \beta}{\partial 1/T} \quad [\text{Eq. 3}]$$

where  $\beta$  is the heating rate and  $T$  the absolute temperature (Fig. 6).

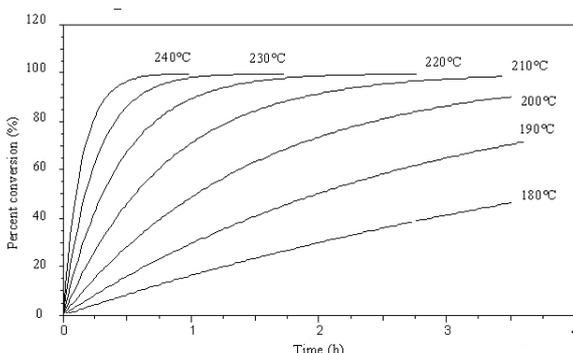
The reaction is called a complex reaction if two or more elementary steps, each having unique activation energies, control the rate of product formation. In such a reaction, a change in the activation energy would be observed as the extent of conversion increase. This change will depend on the contribution of each elementary step, which gives an “effective” activation energy that varies with the extent of the conversion. Kinetic complexities are not limited to multiple chemical steps.

Fig. 7 shows the percent of material convert versus time for a selected temperature. This result allows to determining the advantages of running the reaction at different temperatures. They may also include physical processes having different activation energies.

Fig. 8 shows the TG curves for different heating rates of the EFV obtained in dynamic experiments were used heating rates 5, 7.5, 10,



**Figure 6.** Ozawa plots of EFZ at fractional extent of reaction:  $\alpha = 1.0\%$ ,  $\alpha = 2.5\%$ ,  $\alpha = 5.0\%$ ,  $\alpha = 10\%$  and  $\alpha = 20\%$ .

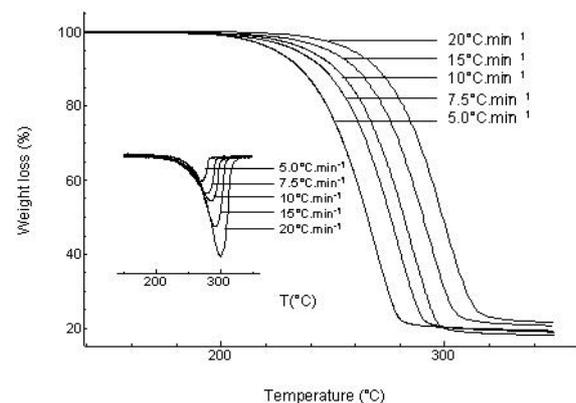


**Figure 7.** The percent of material convert *versus* time for a selected temperature.

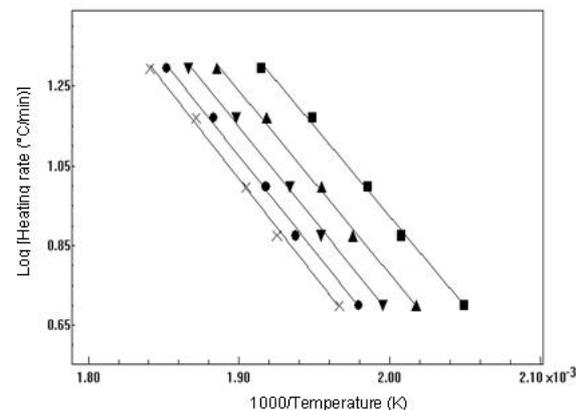
15 and 20 °C·min<sup>-1</sup> obtained in Shimadzu instrument. This Figure show a thermoanalytical profile similar to obtained from TA instrument.

Figures 9 and 10 show the plots obtained and the G(x) graphic function of the inverse temperature for EFV demonstrating good correlation at the five heating rates. These types of plots show a better linear relationship than those taken from the data range of TG curves organized in terms of the plotted range, the initial and final mass range used, and the reaction order assumed.

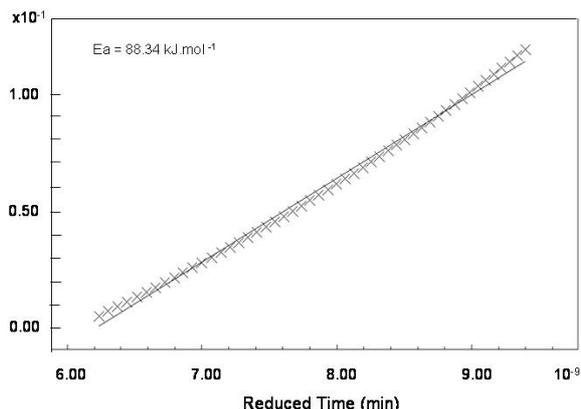
The comparison between activation energies obtained from TA instrument and Shimadzu are listed in Table 2. In addition, the various analytical methods reported in the literature were used in comparison with the kinetic analysis results obtained from the dynamic method. It was found that the dynamic method gave a reliable value of kinetic parameters.



**Figure 8.** Weight loss (TG %) curves of EFZ at different heating rates  $\beta$  (5.0-7.5-10.0-15.0-20.0 °C·min<sup>-1</sup>) using TA-50 Shimadzu instrument.



**Figure 9.** Ozawa plots of EFZ at fractional extent of reaction:  $\alpha = 1.0\%$ ,  $\alpha = 2.5\%$ ,  $\alpha = 5.0\%$ ,  $\alpha = 10\%$  and  $\alpha = 20\%$ .



**Figure 10.** G(x) graphic function of the inverse temperature of the contents of EFV.

Conversion %	Shimadzu Instrument Activation energy (kJ/mol)	TA Instrument Activation energy (kJ/mol)
1.0	79.76	87.41
2.5	82.67	90.06
5.0	84.84	93.97
10.0	88.34	99.62
20.0	93.01	107.79

**Table 2.** Kinetic parameters for EFZ at different conversion levels.

## CONCLUSION

Drug-excipient interaction study at an early stage of product development is an important exercise in the development of a stable dosage form. However, no universally accepted protocol is available for evaluating the compatibility of drug with different excipients. Thermoanalytical results supported as absence of incompatibility using physical mixtures of EFZ and excipients (e.g. croscarmellose, magnesium stearate, microcrystalline cellulose, crospovidone and cellulose 101).

Kinetic parameters such as activation energies,  $E_a$ , and kinetic apparent pre-exponential factor,  $\log Z$ , have been determined from the thermogravimetric data using heating rates 5, 7.5, 10, 15 and 20 °C·min<sup>-1</sup> involving integral (Flynn-Wall-Ozawa's equation) methods. Using the isoconversional method of FWO, the activation energy was determined to be 99.62 kJ/mol (TA Instruments) and 88.34 kJ/mol (Shimadzu Instrument) for the conversion factor of 0.10. The data were examined to determine kinetic parameters using two different approaches. The derived activation energies were found to be dependent on the mathematical equation used.

Non-isothermal methods have been shown to produce different activation energies, and the mathematical treatment of the TGA data may also influence in the activation energy values.

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