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Thermal behavior and decomposition kinetics of efavirenz under isothermal and non-isothermal conditions

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Abstract Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, was approved for the treatment of human immunodeficiency virus type 1 infection (HIV-1), and it is used in the high activity antiretroviral therapy in association with others drugs as the best choice of treatment in adults and children. EFV was investigated about its thermal behavior, through DSC, TG, and DTG techniques, and the kinetic parameters were evaluated by isothermal and non-isothermal conditions by Ozawa's conventional method and by an isoconversional method proposed by Ozawa–Flynn–Wall. The decomposition process was obtained by thermogravimetric curves to determine the kinetic. EFV was melted at $T_{peak} = 411.66$ K, and the decomposition started at 528.97 K. The activation energy values obtained were 93.24 and 91.58 kJ mol^{-1} for the non-isothermal and isothermal conditions, respectively, with the conventional method. The activation energy values obtained by isoconversional method were practically constant, hence the reaction involves a single step.

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Introduction

The non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV), is manufactured by Bristol-Myers Squibb and Merck Sharp & Dohme as Sustiva® [1] and Stocrin® [2], respectively. EFV was approved for the treatment of human immunodeficiency virus type 1 infection (HIV-1) [3, 4], and it is used in the high activity antiretroviral therapy (HAART) in association with other drugs as the best choice of treatment in adults and children [5].

Thermal analysis is a routine method for quality control of drugs and substances of pharmaceutical interest that provides useful information about the physical properties of materials [6–10]. Differential scanning calorimetry (DSC) and thermogravimetric analysis (TG), either separately or together, are often the first step(s) in a comprehensive search for a property of a particular drug and for the determination of its stability, compatibility, and kinetic analysis; moreover, results can be obtained more quickly with small quantities of material and without the use of solvents [11].

The thermal decomposition data obtained by thermogravimetry can be analyzed to obtain kinetic parameters [12, 13]. These parameters can be used in the design and/or improvement of dosage forms. The thermoanalytical technique cannot replace the classical stability studies that usually require weeks or months, but it can provided an early idea to direct the process toward the most successful formulation [9, 13–15].

The objective of this paper is to investigate the thermal behavior and the decomposition kinetics of EFV under

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isothermal and non-isothermal conditions. The kinetic parameters were evaluated from thermogravimetric data by the conventional method of Ozawa and isoconversional method of Ozawa–Flynn–Wall. Finally, the activation energy values obtained by non-isothermal conditions with both conventional and isoconversional methods, were compared.

Experimental

Materials

The micronized EFV (purity >99 %) used in this study was provided by FIOCRUZ.

Methods

Differential scanning calorimetry (DSC)

DSC curves were obtained in a DSC-60 cell (Shimadzu, Kyoto, Japan) using aluminum crucibles with sample of about 2 mg, under dynamic nitrogen atmosphere (50 mL min^{-1}), and heating rate of 10 K min^{-1} in temperature range from 298 to 773 K. DSC cell was calibrated with a standard reference of indium and empty aluminum crucibles were used as reference.

Thermogravimetric analysis (TG)

The TG/DTG measurements were obtained with a thermobalance model TGA-50 (Shimadzu, Kyoto, Japan) in the temperature range of 298–1173 K, using platinum crucibles with sample of 4.5 mg, under dynamic nitrogen atmosphere (50 mL min^{-1}) and heating rate of 10 K min^{-1}.

The Kinetics Committee of the ICTAC published a review of the existing methods for helping to perform reliable kinetic parameters through a combination of non-isothermal and isothermal experiments as the best way to establish kinetic models [16].

The heating rates used for non-isothermal experiments using Ozawa–Flynn–Wall method, were 5, 10, and 20 K min^{-1} to target a temperature of 600 K and the heating rates used for Ozawa's conventional method were 2.5, 5, 10, 15, and 20 K min^{-1} to target a temperature of 673 K. For both methods, a nitrogen atmosphere was used with the flow rate of 50 mL min^{-1}. Samples of approximately 2 mg were weighed in the platinum crucibles.

In the isothermal condition, the temperatures were 423, 433, 443, 453, and 463 K, with 10 K temperature increments, under dynamic nitrogen atmosphere with the flow rate of 50 mL min^{-1}. The isothermal holding was monitored based on the time to a mass loss of 5 % degradation and the experimental data was treated with the application of linear regression. The equipment was preliminary calibrated with standard reference of calcium oxalate [17].

Kinetic procedure for Ozawa's conventional method

The kinetic parameter and the order of reaction for Ozawa's conventional method [18] were obtained with a software TA Menu 1.14 version.

Kinetic procedure for isoconversional method

Kinetic methods consider that the isothermal rate of conversion, $d\alpha/dt$, is a linear function and is a function of two variables: temperature (T) and extent of conversion (α), as shown in Eq. 1 [16].

$$d\alpha/dt = k(T)f(\alpha) \quad (1)$$

Kinetic methods assume that $d\alpha/dt$ 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 [18]. Under non-isothermal conditions, Eq. 1 becomes:

$$d\alpha/f\alpha = (A/\beta)e^{-E/RT}dT \quad (2)$$

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.

According to Muraleedharan et al. [19], the method proposed by Ozawa–Flynn–Wall is an isoconversional method that uses linear regression to calculate E. This method postulates that $f(\alpha)$ does not change with different heating rates for all values of α, thus, measurements of temperature, corresponding to fixed values of α at different heating rates are required. Under these conditions Eq. 2 turns into Eq. 3:

$$\ln \beta = \ln[Af(\alpha)]/[d\alpha/dt] - E/RT \quad (3)$$

and a plot of $\ln \beta$ versus $1/T$ should give a straight line with a slope of $-E/R$.

If the values of E determined for the various values of α are almost constant, then certainly the reaction involves only a single step; on the other hand, a change in E with increasing degree of conversion is an indication of a complex reaction mechanism that invalidates the separation of variables involved in the Ozawa, Flynn, and Wall analysis.

The analysis done by the isoconversional method may corroborate the results obtained for activation energy by Ozawa's method in the non-isothermal conditions. It is well known in the art that the most reliable kinetic methods are the isoconversional ones [16, 18, 20].

Arrhenius parameters and the reaction mechanisms can be determined by kinetic analysis of solid decomposition

through isothermal and non-isothermal kinetic analysis [6, 20–22]. The activation energy can be determined through several thermogravimetric curves obtained at different heating rates by the non-isothermal method.

Results and discussion

Thermal characterization of EFV raw material

Figure 1 represents the TG/DTG and DSC curves of the EFV. The DSC curve shows an endothermic peak corresponding to the melting event ($T_{peak} = 411.66$ K; $T_{onset} = 410.13$ K; $\Delta H_{fusion} = -41.76$ J g^{-1}). The exothermic events in the sequence correspond to the degradation process. Thermal instability up to 528.97 K is evidenced with the DSC data combined with TG. The thermal degradation process occurs in one well defined stage in the temperature range from 528.97 to 567.87 K with mass loss $\Delta m = 95.23$ %.

Kinetic studies

Figure 2 demonstrates the α–T curves for the non-isothermal decomposition of EFV at different heating rates, and the estimated values of E related to thermal decomposition of EFV are given in Table 1. These values were calculated using the Ozawa–Flynn–Wall method [13] by fitting the plots of ln β versus $1/T$. Linear regression was used to obtain the slope and the coefficient of correlation (r) the r values are also presented in Table 1.

The activation energy values obtained for EFV by the isoconversional method in the non-isothermal conditions showed practically constant, relative standard deviation (%RSD = 3 %). The results suggest that the reaction involves a single step.

Figure 3 demonstrates non-isothermal or dynamic kinetic data by plotting mass loss versus temperature. The superposition of five thermogravimetric curves obtained at different heating rates, are shifted to higher temperatures when heating rates increase. A linear tendency is demonstrated by the correlation of the five curves showed

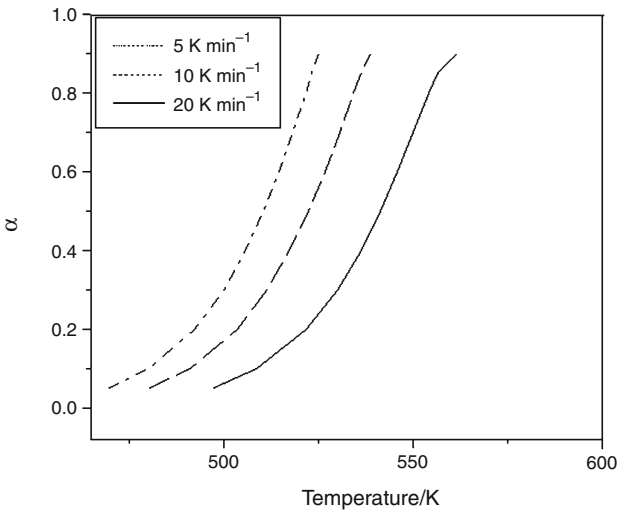

Fig. 2 α–T curve for the decomposition of EFV at different heating rates

Table 1 Activation energies for the 5–90 % conversions for the EFV obtained by the Ozawa–Flynn–Wall method

Conversion/%	E_a/kJ mol^{-1}	r
5	91.17 ± 7.85	0.98
10	91.49 ± 7.00	0.98
20	93.11 ± 4.97	0.98
30	94.30 ± 5.00	0.97
40	94.69 ± 5.02	0.98
50	95.71 ± 5.28	0.98
60	96.17 ± 5.51	0.98
70	96.16 ± 4.58	0.98
80	95.20 ± 4.96	0.98
85	94.01 ± 4.38	0.98
90	85.28 ± 4.45	0.96

E_a activation energy

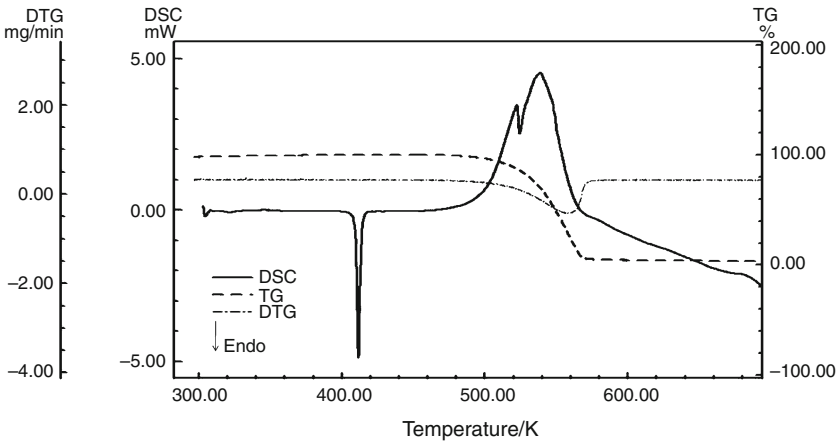

Fig. 1 DSC and TG/DTG curves of EFV obtained in nitrogen atmosphere of 50 mL min^{-1} at a heating rate of 10 K min^{-1}

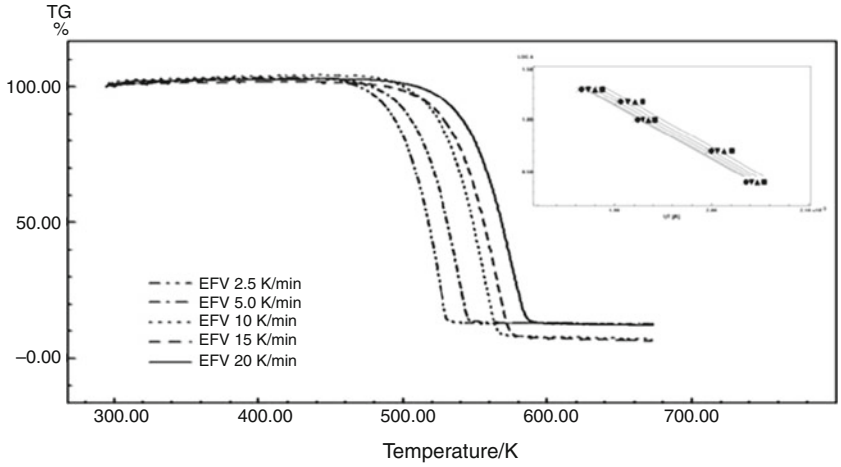

Fig. 3 TG curves of EFV obtained at different heating rates under dynamic nitrogen atmosphere. The *inset* figure shows Ozawa's plot with correlation of the five curves presenting a linear tendency

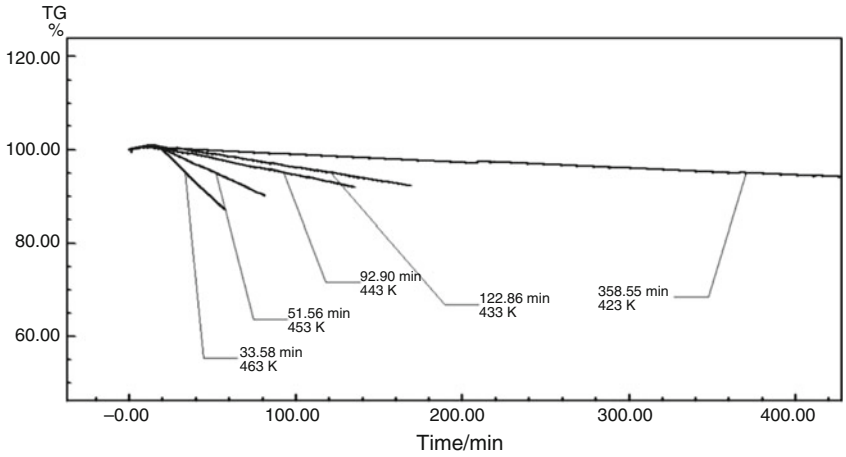

Fig. 4 Isothermal TG curves of EFV obtained between 463, 453, 443, 433, and 423 K, under a nitrogen atmosphere with a flow rate of 50 mL min^{-1}

in the inserted figure. The activation energy (E), Arrhenius frequency factor (A) and order of reaction (n) were determined by Ozawa's conventional method. The activation energy was obtained from a plot of logarithms of heating rates as a function of the inverse of temperature ($1/T$) for a constant $G(x)$, where $G(x)$ is the integrated form of the conversion dependence function, $f(x)$.

The kinetics parameters obtained were: activation energy (E) of 93.24 kJ mol^{-1}, frequency factor (A) of 1.672×10^8 min^{-1}, and zero order reaction ($n = 0$).

The isothermal curves obtained are illustrated in Fig. 4, and show mass loss rate in function of time. The isothermal studies were investigated using five temperatures at 463, 453, 443, 433, and 423 K. The higher the temperature the lower the time necessary for the same mass loss to occur. At the isothermal curve at 463 K, it took 33.58 min for a decline of 5 % of the mass, while at the isothermal curve at 423 K, it took 358.55 min. The natural logarithm of time ($\ln_t$) corresponding to a certain mass loss ($\alpha = 5$ %) is linearly dependent on the reciprocal of temperature T. The graph in Fig. 5 was constructed applying the isothermal condition by the conventional Ozawa's method ($\ln_t$ vs. $1/T$) each time with its respective temperature. The equation obtained from this linear regression method was $y = -11.016x + 20.356$ with $R^2 = 0.9634$ and it showed that the order of reaction remains constant ($n = 0$) within the temperature and mass loss interval under consideration.

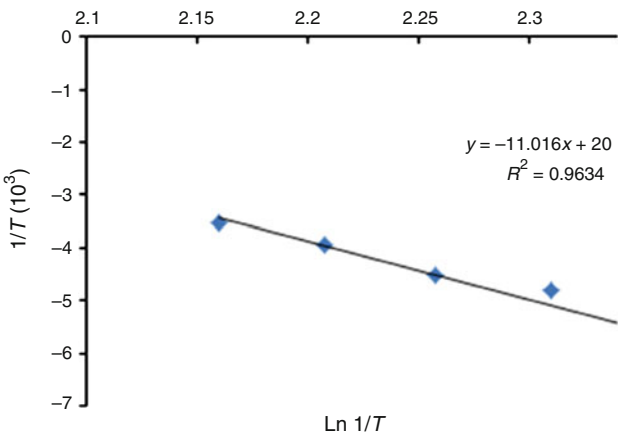

Fig. 5 Plot ln $1/t$ versus the reciprocal of temperature $1/T$ from the data obtained in isothermal TG curves

The activation energy was calculated from the slope of the line, from linear regression. The calculus is done by the product of 11.016 with the molar gas constant ($R = 8.314$). The calculated energy from this method was $E = 91.58$ kJ mol^{-1}.

The decomposition kinetics for isothermal conditions occur in constant rate, zero order, and is independent from the concentration of the reactants.

Both values obtained by Ozawa's conventional method using isothermal and non-isothermal conditions were similar. The combined experiments using isothermal and non-isothermal conditions is the best way to properly determine kinetic parameters [16]. However the use of only one value for the activation energy does not allow for the detection of differences in E with the extent of conversion. That was possible to determine with the isoconversional method and in the case of EFV the activation energy values were similar, therefore unconsidered by the TA menu software.

Conclusions

The thermal analytic behavior of EFV showed melting point at 411.66 K and thermal stability until 528.97 K. The activation energy values obtained for EFV by isoconversional method in the non-isothermal conditions appeared practically constants, (%RSD = 3 %) and suggest that the reaction involves a single step. The activation energy values obtained by isothermal and non-isothermal conditions calculated by Ozawa's conventional method were similar. However, these values do not allow for any conclusions about the degradation process. The correct method of Ozawa is the isoconversional procedure to identify the dependence of the activation energy on the degree of conversion, α. In the isoconversional method, the reaction model is not dependent on temperature or heating rate. In the solid state reactions, the activation energy E is dependent on the degree of conversion α, that is, E is variable. The kinetic Ozawa method developed in the software packages was applied to an investigation and comparison; however, it is not recommended because the isoconversional procedure is not implemented in these packages and the use of conventional Ozawa's method can cause inaccuracies.

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References

1. FDA. In: CDER Fast Track Products Approved Since 1998 through June 1, 2010. 2010. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM216527.pdf. Accessed 15 Dec 2010.
2. ANVISA. Agência Nacional de Vigilância Sanitária. In: Resolução—RE 1229 de 14 de agosto de 2001. 2001. http://www.anvisa.gov.br. Accessed 15 Dec 2010.
3. Ribeiro JAA, Campos LMM, Alves RJ, Lages GP, Pianetti GA. Efavirenz related compounds preparation by hydrolysis procedure: setting reference standards for chromatographic purity analysis. J Pharm Biomed. 2007;43:03–298.
4. Sathigari S, Chadha G, Lee YP, Wright N, Parsons DL, Rangari VK, Fasina O, Babu RJ. Physicochemical characterization of efavirenz—cyclodextrin inclusion complexes. AAPS Pharm Sci Technol. 2009;10(1):81–7.
5. Chiappetta DA, Lorenzo CA, Rico AR, Taboada P, Concheiro A, Sosnik A. *N*-alkylation of poloxamines modulates micellar encapsulation and release of the antiretroviral efavirenz. Eur J Pharm Biopharm. 2010;76:24–37.
6. Cides LCS, Araújo AAS, Filho MS, Matos JR. Thermal behavior, compatibility study and decomposition kinetics of glimepiride under isothermal and non-isothermal conditions. J Therm Anal Calorim. 2006;84(2):441–5.
7. Leite RS, Macedo RO, Torres SM, Batista CCN, Baltazar LO, Neto SAL, Souza FS. Evaluation of thermal stability and dissolution of nifedipine crystals. J Therm Anal Calorim. 2013;111:2117–23.
8. Tiţa B, Marian E, Fuliaş A, Jurca T, Tiţa D. Thermal stability of piroxicam. Part 2. Kinetic study of the active substance under isothermal conditions. J Therm Anal Calorim. 2013;112:367–74.
9. Perpétuo GL, Gálico DA, Fugito RA, Castro RAE, Eusébio MES, Treu-Filho O, Silva ACM, Bannach G. Thermal behavior of some antihistamines. J Therm Anal Calorim. 2013;111:2019–28.
10. Tita B, Jurca T, Tita D. Thermal stability of pentoxifylline: active substance and tablets. Part 1. Kinetic study of the active substance under non-isothermal conditions. J Therm Anal Calorim. 2013;1–9.
11. Yu L, Reutzel SM, Stephenson GA. Physical characterization of polymorphic drugs: an integrated characterization strategy. Pharm Sci Technol Today. 1998;3:118–27.
12. Aquino FM, Melo DMA, Santiago RC, Melo MAF, Martinelli AE, Freitas JCO, Araújo LCB. Thermal decomposition kinetics of PrMO3 (M = Ni or Co) ceramic materials via thermogravimetry. J Therm Anal Calorim. 2011;104:701–5.
13. Tiţa D, Fuliaş A, Tiţa B. Thermal stability of ketoprofen. Part 2. Kinetic study of the active substance under isothermal conditions. J Therm Anal Calorim. 2013;111:1979–85.
14. Rodante F. Multi-step decomposition process for some antibiotics A kinetic study. Thermochim Acta. 2002;394:7–18.
15. Chaves LL, Rolim LA, Gonçalves MLCM, Vieira ACC, Alves LDS, Soares MFR, Soares-Sobrinho JL, Lima MCA, Rolim-Neto PJ. Study of stability and drug-excipient compatibility of diethylcarbamazine citrate. J Therm Anal Calorim. 2013;111:2179–86.
16. Vyazovkin S, Burnham AK, Criado JM, Maqueada-Pérez LA, Popescu C, Sbirrazzuoli N. ICTAC kinetic committee recommendations for performing kinetic computations on thermal analysis data. Thermochim Acta. 2011;520:1–19.
17. Murakami FS, Bernardi LS, Pereira RN, Valente BR, Vasconcelos EC, Filho MASC, Silva MAS. Comparative behavior studies of cinnamic acid using isothermal and nonisothermal kinetic methods. Pharm Chem J. 2009;43(12):716–20.
18. Ozawa T. Thermal analysis—review and prospect. Thermochim Acta. 2000;355:35–42.
19. Muraleedharan K, Kannan MP, Devi TG. Thermal decomposition kinetics of potassium iodate. J Therm Anal Calorim. 2011;103:943–55.
20. Mothé CG, Miranda IC. Study of kinetic parameters of thermal decomposition of bagasse and sugarcane straw using Friedman and Ozawa–Flynn–Wall isoconversional methods. J Therm Anal Calorim. 2013;1–9.

21. Málek J, Koga N, Pérez-Maqueda LA, Criado JM. The Ozawa's generalized time concept and YZ-master plots as a convenient tool for kinetic analysis of complex processes. J Therm Anal Calorim. 2013;1–10.

22. Han Y, Li T, Saito K. A modified Ortega method to evaluate the activation energies of solid state reactions. J Therm Anal Calorim. 2013;112:683–7.