



Thermoanalytical and Kinetic Studies for the Thermal Stability of Nimesulide Under Different Heating Rates

AHMED A. M. AHMED¹, AML M. ASRAN¹ and MONA A. MOHAMED^{2*}

¹Deanship of Common First Year, Jouf University, P.O. Box 2014, Sakaka, Saudi Arabia.

²Pharmaceutical Chemistry Department, National Organization for Drug Control and Research, Egyptian Drug Authority (EDA), Giza, Egypt.

*Corresponding author E-mail: monagamall77@gmail.com

<http://dx.doi.org/10.13005/ojc/380215>

(Received: January 06, 2022; Accepted: March 01, 2021)

ABSTRACT

The elucidation of the thermal stability and degradation of pharmaceutical drugs utilized in medication is commonly conducted using thermal examination techniques. Kinetic studies have emerged as a critical component of thermal analysis, with the primary goal of determining the kinetic approach of degradation and calculating the Arrhenius equation parameters. The current study describes the thermal behaviour of nimesulide, and the calculation of the melting point using thermoanalytical graphs, as well as the identification of parameters of the decomposition kinetic. The kinetic investigation of nimesulide's active substance's, thermal degradation was carried out in a nitrogen environment via non-isothermal parameters at four rates of heating: 5, 10, 15, 20, and 20°C/minute. The kinetic models of the thermal breakdown pathway were calculated from TG/DTG graphs using differential approaches of Friedman isoconversional method and integral approaches such as the Ozawa, and Starink method.

Keywords: Nimesulide, Kinetic parameters, Thermal stability, Decomposition, Quality control.

INTRODUCTION

Nimesulide (4-nitro-2-phenoxy methane sulfonamide) has a nitroaromatic ring and is extensively used as a nonsteroidal anti-inflammatory (NSAID) medication that specifically inhibits prostaglandin formation¹. Furthermore, nimesulide contains antipyretic and analgesic characteristics that may be used to treat rheumatoid arthritis, prostatovesiculitis, and osteoarthritis².

Thermal analysis is a common quality control

tool for pharmaceutical medications and chemicals that offers important facts regarding the physical characteristics of materials^{3,4}. Thermogravimetric analysis (TG) is frequently the gateway in the comprehensive exploration for a specific drug's characteristic and for determining its compatibility in single form or in the presence of other constituents, thermal stability, and kinetic examination. Additionally, with minimal amounts of material and without the use of solvents, results may be reached rapidly⁵. The thermogravimetry data collected by thermal decomposition may be evaluated to derive kinetic



parameters. The use of thermoanalytical methods may yield fresh insights into the temperature and energy involved with phenomena like melting, glass transition, oxidation reactions, decomposition, crystallisation, or crystal transition⁶.

The thermal degradation of pharmaceuticals is significant because it may be used to anticipate degradation (decomposition) rates at lower values of heating using data from accelerated routes investigated at high temperatures. The temperature might raise the temperature of chemical processes, supplying enough activation energy to disruption the chemical links and start the degradation pathway. Understanding of such variables are useful for elucidating incompatibility and the influence on the stability in both pure pharmaceuticals and drug-excipient combinations.

Nimesulide is determined using different techniques including liquid chromatography⁷⁻⁹, spectrophotometry¹⁰⁻¹², and electrochemical methods¹³⁻¹⁷.

The purpose of this research is to look at the thermal behaviour and kinetics of nimesulide decomposition using non-isothermal settings at changed heating rates. Moreover, to the best of our knowledge, no information regarding the nimesulide's thermal characteristics or degradation kinetics.

EXPERIMENTAL

Materials

Nimesulide was offered from Pharaonia Co., Alex, Egypt, and the purity is 99.36%.

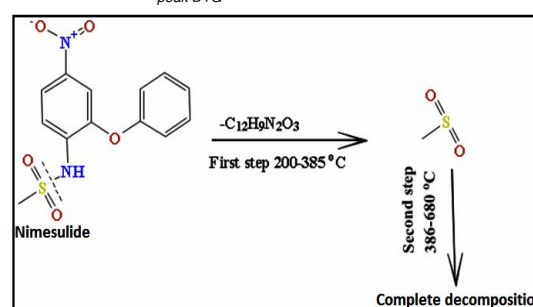
Apparatus

Simultaneous Shimadzu Thermogravimetric Analyzer TGA-60 H with TA 60 software was used to perform thermogravimetry and differential thermal analysis in a platinum crucible in a dry nitrogen environment via a flow rate of 30 mL minute⁻¹. The studies were carried out at various heating speeds from room temperature to 800°C. (5, 10, 15 and 20°C minute⁻¹). Without any additional treatment, the drug mass was around 5 mg of the nimesulide. TG/DTG curves were used to derive decomposition kinetic parameters.

RESULTS AND DISCUSSION

Thermal behavior of nimesulide

The thermoanalytical graphs that define the thermal demeanor of nimesulide in raised temperature setting with a rate of heating of 5°C/min under N₂ gas environment are displayed in Fig. 1. By depicting the TG/DTG plots, two distinct steps with different mass loss are presented. The first stage corresponds to the loss of -C₁₂H₉N₂O₃ ($\Delta m = 74.35\%$) and happens between 210°C to 385°C, with T_{peak DTG} = 305°C.



Scheme 1. The suggested thermal degradation of nimesulide

In the temperature range 386-680°C, the second disintegration phase shows a mass loss ($m = 25.65\%$), indicating full nimesulide decomposition.

The DTA plot represents a significant thermal occurrence across the studied range of temperature.

The endothermic event at 145°C¹⁸ is most probable owing to nimesulide melting, whereas the exothermic event at 320°C is described to the first breakdown course linked with the 1st mass loss shown in the TG/DTG curve as shown in Fig. 2. A significant exothermic peak is detected at 610°C due to the complete pyrolysis of nimesulide. The proposed nimesulide thermal breakdown is best exemplified in Scheme 1.

Effect of heating rate

Figure 2 depicts nimesulide weight-loss curves at various heating speeds ranging from 5 to 20°C/minute. When shown in the graph, as the heating rate rises, the T_{max} values move to higher values. Furthermore, the curves show that nimesulide breakdown occurs in a two phase, with no evolution of water contents at the start of the process.

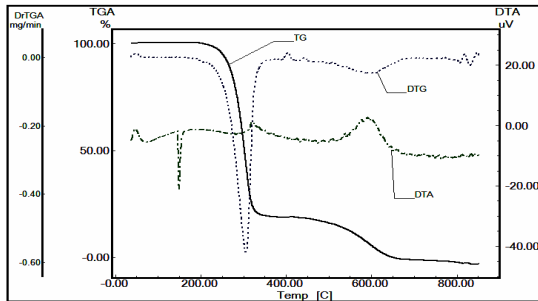


Fig. 1. Thermogravimetric analysis, TG/DTG with DTA graphs of nimesulide under dynamic N₂ gas atmosphere (30 mL min⁻¹) using heating rate at 5°C/minute

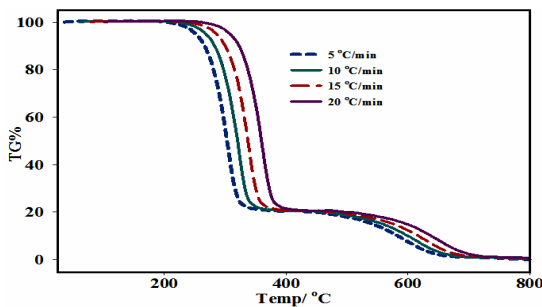


Fig. 2. Thermograms of nimesulide in nitrogen atmosphere at different heating rates

Differential thermal analysis data for the decomposition of nimesulide at various rates of heating is depicted in Fig. 3. The melting point events and disintegration temperatures of the medications were found to be moved to upper temperatures by increasing the heating rate.

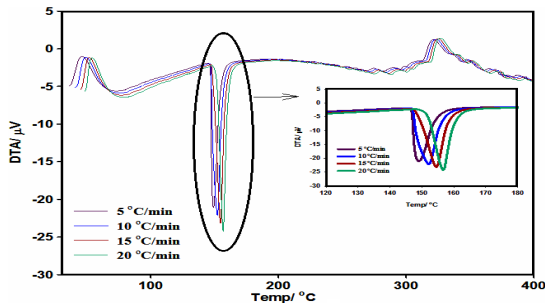


Fig. 3. DTA curves of nimesulide at different heating rates

Kinetic models

The kinetic factors found from the current studies done using non-isothermal circumstances were utilized to evaluate the nimesulide thermal stability. The following kinetic models were used to determine the moving strictures using the TG/DTG graphs: Friedman (Fd)^{19,20}, Flynn-Wall-Ozawa (FWO)²¹⁻²³, and Starink (St)²⁴.

Usually, the kinetics of processes (such as

polymerization, crystallisation, decomposition, etc) may be delineated using rate equations^{25,26}.

$$d\alpha/dt = k(T).f(\alpha) = A. \exp\left(-\frac{E}{R.T}\right).f(\alpha) \quad (1)$$

Where *t* is referring to the time, *k*(*T*) is referring to the Arrhenius rate constant, *α* is referring to the degree of conversion, *A* is referring to the pre-exponential factor and *E* is defining the activation energy, *R* is referring to the universal gas constant, and *f* (*α*) is defining the reaction model related to a the persuaded decomposing pathway. Utilizing non-isothermal settings, the term *dα/dt* is converted with *βdα/dT*, where *β* is referring to the rate of heating, yielding:

$$\beta. \frac{d\alpha}{dT} = A. \exp\left(\frac{E}{R.T}\right).f(\alpha) \quad (2)$$

Friedman (Fd) method

The isoconversional Friedman technique is dependent on the generic reaction rate relation (3),

$$\ln \frac{\beta}{T\alpha^k} = -B \frac{E\alpha}{R.T\alpha} + C \quad (3)$$

Where *B* and *C* are constants. The rate equation is transformed into.

$$\ln\left(\beta \frac{d\alpha}{dT}\right) = \ln[A.f(\alpha)] - \frac{E}{R.T} \quad (4)$$

The graphical depiction of *dα/dt* versus 1/*T* for = const. and varying heating rates (*β*) give rise to straight lines, their slope is defined *E*. A sequence of straight lines, known as the Friedman diagram, is obtained for various values of Figure 3).

Flynn–Wall–Ozawa (F–W–O) approach

Flynn–Wall–Ozawa is considered as one of the integral isoconversional approaches that uses the integral relation of the rate as well as the Doyle approximation for *p* (*x*):

$$\ln\beta = -1.052. \frac{E\alpha}{R. T\alpha} + C \quad (5)$$

For *α* = const., plotting *lnβ* according to 1/*T* yields a straight line relation and the energy of activation (*E*) could be obtained from the slope. A straight family is obtained for various values of Fig. 4. When the heating rate is increased, there is a variation in the mechanism or the rate-determining step. Table 1 shows the activation energy (*E*) values.

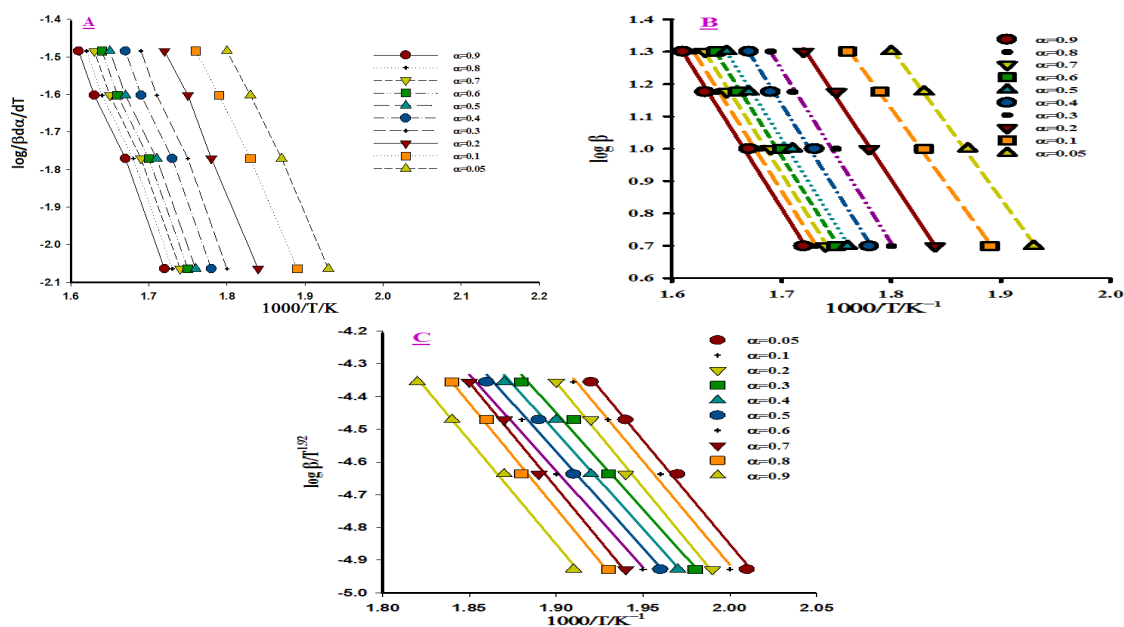


Fig. 4. Plot of Friedman's for nimesulide at variant heating rates (A), The Flynn–Wall–Ozawa (B), and Starink (C) plots

Starink (St) method

St proposes the following estimation for the integral temperature:

$$p(x) = \exp\left(\frac{-1.0008x - 0.312}{x^{1.92}}\right) \quad (5)$$

The values of E were estimated using the Starink technique from the slope of the fitted relation of $\ln(\ln \frac{\beta}{T^{1.92}})$ vs $1/T$ (Fig. 4C) and are presented in Table 1.

The obtained observations have been made based on the collected results include that the

activation energies determined via the Fd approach, FWO, and Starink techniques are quite similar throughout the whole decomposition fraction range. These findings are consistent with the published data on the accuracy offered by these approaches. The activation energy (E) values obtained by these approaches are in worthy convention, and the low fluctuation of E vs. designates a unistadial, yet complicated decomposition pathway. Given that 65% of the E vs. α amount identified in the literature are in the 100 to 230 kJ mol^{-1} range, the E values revealed a significant thermal stability of the nimesulide-active chemical²⁷.

Table 1: Nimesulide calculated activation energy values using Friedman (Fd), Flynn–Wall–Ozawa (FWO), and Starink (ST) approaches

Technique	E/kJ mol ⁻¹ , for conversion degree, α									
	0.05	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
FR	133.0	138.1	137.1	138.8	137.1	139.6	137.5	139.1	139.2	133.2
FW	129.6	129.94	130.19	130.61	130.61	130.77	130.94	131.07	131.19	129.69
Starink	131.6	130.7	130.9	131.1	130.6	131.3	132.1	132.1	132.2	131.6

CONCLUSION

Nimesulide was exposed to a thermal examination in an inert nitrogen environment under non-isothermal circumstances. The thermal stability of nimesulide was investigated in this work utilising thermal techniques and kinetic analysis. Its thermal behaviour was monitored

for this purpose, and a kinetic analysis was carried out to estimate the activation energy. The way nimesulide reacts to heat demonstrates a high degree of thermal stability (up to 210°C). Differential techniques (Fd technique) and integral approaches were utilized to calculate the kinetic parameter values. According to the findings, nimesulide decomposition happens in two steps.

The values of thermodynamic functions calculated using differential and integral approaches were found to be in good agreement. This demonstrates the precision of the techniques used. The computed activation energy might be particularly valuable throughout the drug quality control and preformulation stages of manufacture.

ACKNOWLEDGEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

- Davis R.; Brogden R. N., *Drugs.*, **1994**, *48*, 431-54.
- Haraoui B.; Pelletier J. P.; Cloutier J. M.; Faure M. P.; Martel-Pelletier J., *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology.*, **1991**, *34*, 153-63.
- Mohamed M. A.; Attia A. K., *Journal of Thermal Analysis and Calorimetry.*, **2017**, *127*, 1751-6.
- Mohamed M. A.; Atty S. A.; Banks C. E.; *Journal of Thermal Analysis and Calorimetry.*, **2017**, *130*, 2359-67.
- Fandaruff C.; Araya-Sibaja A.; Pereira R.; Hoffmeister C.; Rocha H.; Silva M., *Journal of Thermal Analysis and Calorimetry.*, **2014**, *115*, 2351-6.
- Salama N. N.; Mohammad M. A.; Fattah T. A., *Journal of Thermal Analysis and Calorimetry.*, **2015**, *120*, 953-8.
- Chandran S.; Ravi P.; Jadhav P. R.; Saha R. N., *Analytical Letters.*, **2008**, *41*, 2437-51.
- Khaksa G.; Udupa N., *Journal of Chromatography B: Biomedical Sciences and Applications.*, **1999**, *727*, 241-4.
- Patravale V. B.; D'Souza S.; Narkar Y., *Journal of Pharmaceutical and Biomedical Analysis.*, **2001**, *25*, 685-8.
- Altinöz S.; Dursun Ö. Ö., *Journal of Pharmaceutical and Biomedical Analysis.*, **2000**, *22*, 175-82.
- Chandran S.; Saggar S.; Priya K. P.; Saha R. N., *Drug Development and Industrial Pharmacy.*, **2000**, *26*, 229-34.
- Upadhyay K.; Asthana A.; Tiwari N.; Mathew S. B., *Research on Chemical Intermediates.*, **2013**, *39*, 3553-63.
- Deroco P. B.; Rocha-Filho R. C.; Fatibello-Filho O., *Talanta.*, **2018**, *179*, 115-23.
- Łysoń M.; Górská A.; Paczosa-Bator B.; Piech R., *Electrocatalysis.*, **2021**, *12*, 641-9.
- Shetti N. P.; Malode S. J.; Bukkitgar S. D.; Bagihalli G. B.; Kulkarni R. M.; Pujari S. B., *Materials Science for Energy Technologies.*, **2019**, *2*, 396-400.
- Wang C.; Shao X.; Liu Q.; Qu Q.; Yang G.; Hu X., *Journal of Pharmaceutical and Biomedical Analysis.*, **2006**, *42*, 237-44.
- Wong A.; Santos A. M.; Fatibello-Filho O., *Journal of Electroanalytical Chemistry.*, **2017**, *799*, 547-55.
- Constantinescu I. C.; Florea M.; Arama C-C.; Nedelcu A.; Monciu C-M, *Farmacia.*, **2009**, *57*, 267-71.
- Friedman H. L., *Journal of Polymer Science Part C: Polymer Symposia*; Wiley Online Library., 1964.
- Friedman H. L., *Journal of Polymer Science Part B: Polymer Letters.*, **1969**, *7*, 41-6.
- Flynn J. H.; Wall L. A., *J Res Nat Bur Stand.*, **1966**, *70*, 487-523.
- Flynn J. H.; Wall L. A., *Journal of Polymer Science Part B: Polymer Letters.*, **1966**, *4*, 323-8.
- Ozawa T., *Bulletin of the chemical society of Japan.*, **1965**, *38*, 1881-6.
- Starink M., *Thermochimica Acta.*, **2003**, *404*, 163-76.
- Brown M., *Thermal Decomposition of Ionic Solids.* Elsevier Science., **1999**.
- Brown M. E.; Dollimore D.; Galwey A. K., *Reactions in the solid state.* Elsevier., **1980**.
- Galwey A. K., *Thermochimica acta.*, **1994**, *242*, 259-64.