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Thermal behavior of drugs

Investigation on decomposition kinetic of naproxen and celecoxib

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Abstract Data on the thermal stability of drugs was required to obtain information for handling, storage, shelf life and usage. In this study, the thermal stability of two nonsteroidal anti-inflammatory drugs (NSAIDs) was determined by differential scanning calorimetry (DSC) and simultaneous thermogravimetery/differential thermal analysis (TG/DTA) techniques. The results of TG analysis revealed that the main thermal degradation for the naproxen and celecoxib occurs in the temperature ranges of 196–300 and 245–359 °C, respectively. The TG/DTA analysis of compounds indicates that naproxen melts (at about 158.1 °C) before it decomposes. However, the thermal decomposition of the celecoxib started about 185 °C after its melting. The influence of the heating rate (5, 10, 15, and 20 °C min^{-1}) on the DSC behavior of the both drug samples was verified. 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 and frequency factor for the compounds were obtained from the DSC data by non-isothermal methods proposed by ASTM E696 and Ozawa. Based on the values of activation energy obtained by various methods, the following order for the thermal stability was noticed: naproxen > celecoxib. Finally, the values of $\Delta S^{\#}$, $\Delta H^{\#}$, and $\Delta G^{\#}$ of their decomposition reaction were calculated.

Keywords Non-isothermal · DSC · TG/DTA · Thermal stability · Drug · NSAIDs · Activation energy

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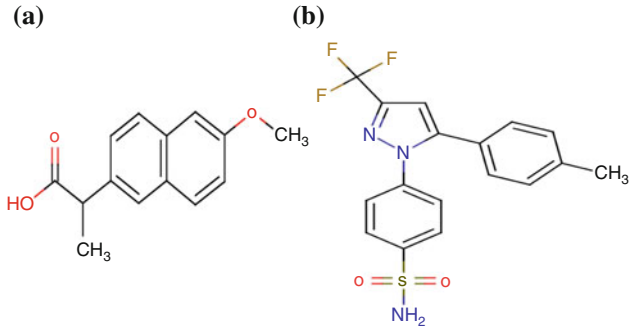
Introduction

Naproxen or 2-(6-methoxynaphthalen-2-yl) propanoic acid ($C_{14}H_{14}O_3$) belongs to a group of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). It works by reducing hormones that cause inflammation and pain in the body. Naproxen is used to treat pain or inflammation caused by conditions such as arthritis, ankylosing spondylitis, tendinitis, bursitis, gout, or menstrual cramps [1, 2].

Also, celecoxib (Celebra; Celebrex; Niflam) or 4-[5-(4-methylphenyl)-3-trifluoromethyl)-1H-pyrazol-yl]benzenesulfonamide ($C_{17}H_{14}F_3N_3O_2S$) belongs to nonsteroidal anti-inflammatory drugs (NSAIDs). It works by reducing hormones that cause inflammation and pain. Celecoxib is used to treat pain or inflammation caused by many conditions such as arthritis, ankylosing spondylitis, and menstrual pain [3–7]. It is also used in the treatment of hereditary polyps in the colon. Scheme 1 shows chemical structures of these drugs.

Thermal analytical techniques can provide important information regarding storage and stability of pharmaceuticals. Also, kinetic parameters obtained from thermoanalytical data are highly useful for making predictions of performance parameters of drugs, for example, "shelf life." On the other hand, understanding the response of drugs and their formulations to thermal stresses is an integral part of the development of stable medicinal products. Thermal analytical methods have thus become important tools for the development of modern medicines [8–12]. These are precise and accurate techniques with low sample requirements, and can provide detailed information about new chemical entities even at the very earliest stages of discovery and development of the new compositions and drugs [13–16].

One main purpose for the kinetic analysis of solid decomposition is to determine the reaction mechanism(s)



Scheme 1 Chemical structure of **a** naproxen and **b** celecoxib

and to calculate the Arrhenius parameters [17–20]. There are two ways to achieve this, one uses isothermal kinetic analysis while the other uses non-isothermal kinetic analysis. The disadvantages and advantages of determining kinetic parameters by non-isothermal methods rather than by conventional isothermal studies are summarized by Wendlandt [21, 22].

In this study, the naproxen and celecoxib drugs were investigated by means of differential scanning calorimetry (DSC) and simultaneous thermogravimetry/differential thermal analysis (TG/DTA). The results allowed us to acquire information concerning these compounds in the solid state, including their thermal stability and thermal decomposition. Also, this study seeks for determination of kinetic parameters of non-isothermal decomposition of the compounds. To the best our knowledge, there is no previous report on the thermal behavior of these drugs.

Experimental

Naproxen and celecoxib, pharmaceutical grade min. 99.5% (Abureihan Pharma, Iran) were used without further purification. The DSC graphs were obtained by Du Pont differential scanning calorimeter model DSC 910S, in temperature range of 50–500 °C using an aluminum crucible, at different heating rates (5, 10, 15, and 20 °C min^{-1}), under nitrogen atmosphere with the flow rate of 50 mL min^{-1}.

Thermogravimetry (TG) and differential thermal analysis (DTA) were carried out using a Stanton Redcroft, STA-780 series with an aluminum crucible, applying heating rate of 10 °C min^{-1} in a temperature range of 50–600 °C, under nitrogen atmosphere with the flow rate of 50 mL min^{-1}. The sample mass used was about 3.0 mg.

Results and discussion

The thermoanalytical graphs of naproxen are presented in Fig. 1a. The TG/DTA graphs obtained in nitrogen

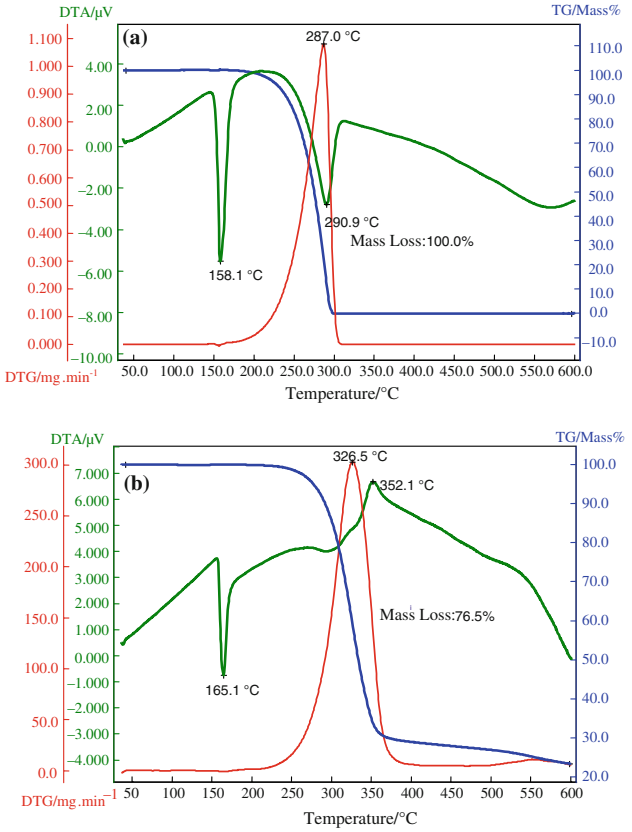


Fig. 1 TG/DTA curves for drug samples **a** naproxen and **b** celecoxib; sample mass 3.0 mg; heating rate 10 °C min^{-1}; nitrogen atmosphere

atmosphere showed an endothermic behavior commencing near 158.1 °C, which is the melting point of naproxen. Up to the melting point, the naproxen is thermally stable. However, at higher temperatures, naproxen presents a main mass loss step between 196 and 300 °C, which in this step $\Delta m = 100\%$. The DTA curve showed a broad endothermic behavior in this temperature range, which is the decomposition of this drug ($T_{\text{peak DTA}} = 290.9$ °C).

The simultaneous TG/DTA curves obtained in nitrogen atmosphere for the celecoxib are shown in Fig. 1b. According to the TG/DTA data, an endothermic peak was observed about 165.1 °C corresponding to the melting point of celecoxib. The mass loss ($\Delta m = 76.5\%$) is in the range 245–360 °C, which occurs in a single step. During this step, a relatively sharp and continuous mass loss over 250 °C was observed until 360 °C. Table 1 summarizes the experimental results of TG/DTA obtained for each compound.

Effect of heating rate

Table 2 shows DSC curves for the decomposition of naproxen and celecoxib at several heating rates. It was found that, by increasing the heating rate, the melting peaks

Table 1 Summary of TG/DSC results

Component	Transition temperature/°C			Mass loss/%
	Melting	Decomposition	T^*	Δm
Naproxen	158.1 (±0.1)	290.9 (±0.2)	196–300	100
Celecoxib	165.1 (±0.3)	352.1 (±0.1)	245–359	76.5

T^* is the temperature when there is fall in a sample's mass

and the decomposition temperature of the drugs were shifted to higher temperatures.

Kinetic methods

The ASTM method E698 [23] occupies intermediate position between the model-fitting and model-free methods. It uses a model-free estimate for the activation energy which is evaluated from Kissingers plot of ln ($\beta\ T_m^{-2}$) against $1/T_m$ [24], where T_m is the temperature corresponding to the maximum of $d\alpha/dT$. In this study, ASTM method was used to determine the Arrhenius parameters for the thermal decomposition of naproxen and celecoxib. In order to calculate the pre-exponential factor (Z), it was assumed that the decomposition followed first-order kinetics. Table 2 summarizes the experimental results as well as the maximum peak temperatures (T_m) for each compound and heating rates (β) used to perform the calculations in the ASTM E698 method.

The plot of the ln ($\beta\ T_m^{-2}$) against $1/T_m$ was straight lines (Table 3) for naproxen ($r = 0.9975$) and celecoxib ($r = 0.9951$), which indicated that the mechanism of thermal decomposition of these compounds over this temperature range did not vary. The slope of the lines was equal to $-E_a/R$. Therefore, the activation energy (E_a) was obtained from the slope of the graph while the log of the pre-exponential factor, log (Z/s^{-1}) was calculated from the expression given in ASTM E698: $Z = \beta\ (E_a/RT_m^2)\ \exp\ (E_a/RT_m)$. Table 3 contains the calculated values of activation energy and frequency factors for both compounds.

Activation energy (E_a) for these compounds was calculated by Ozawa method [25, 26].

In this method, activation energy could be determined from plots of the logarithm of the heating rate versus the inverse of the temperature at the maximum reaction rate in constant heating rate experiments. The activation energy can be determined by Ozawa method without a precise knowledge of the reaction mechanism, using the following equation:

$$\log \beta + 0.496 E_a/RT_m = C. \quad (1)$$

The plot of logarithm of heating rates versus reciprocal of the absolute peak temperature for naproxen and celecoxib was straight lines with $r = 0.9985$ and 0.9961, respectively. On the other hand, frequency factor (Z) was found for both compounds from the following relation [27]:

$$Z = \beta E \exp(E/RT_m)]/RT_m^2.$$

All resulting data are summarized in Table 3. Comparing the results of the application of the two methods, we observe that values calculated for both compounds by Ozawa method are slightly higher than those of ASTM method. However, both methods reveal the same trend of activation energies for the whole conversion range studies.

After obtaining the kinetic parameters E and A, the thermodynamic parameters of activation can be calculated from the following equations [28, 29]:

Table 2 Melting point and decomposition temperature of naproxen and celecoxib obtained by DSC at various heating rate

Compound	Naproxen		Celecoxib	
Heat flow/°C min^{-1}	Melting point/°C	Decomposition temperature/°C	Melting point/°C	Decomposition temperature/°C
5	152.0 (±0.2)	268.5 (±0.1)	159.1 (±0.2)	337.5 (±0.2)
10	158.1 (±0.1)	290.9 (±0.2)	165.1 (±0.3)	352.1 (±0.1)
15	166.1 (±0.3)	299.6 (±0.3)	169.5 (±0.2)	363.5 (±0.1)
20	173.0 (±0.2)	308.7 (±0.2)	175.5 (±0.2)	368.7 (±0.2)

Table 3 Comparison of kinetic parameters of the drug samples obtained by ASTM and Ozawa methods

Drug sample	Method	E_a/kJ mol^{-1}	Log Z/s^{-1}	Linear regression (r)	$\Delta G^{\#}$/kJ mol^{-1}	$\Delta H^{\#}$/kJ mol^{-1}	$\Delta S^{\#}$/J mol^{-1}	Log K/s^{-1}
Naproxen	ASTM	81.4 (±0.2)	7.1 (±0.02)	0.9951	146.3	76.7	−123	−7.18
	Ozawa	86.7 (±0.3)	7.6 (±0.04)	0.9961	146.0	82.0	−113	−7.61
Celecoxib	ASTM	130.9 (±0.4)	10.5 (±0.05)	0.9975	161.8	125.7	−58	−12.46
	Ozawa	134.1 (±0.2)	10.8 (±0.02)	0.9985	161.8	128.9	−53	−13.24

r Linear regression coefficient

$\Delta G^{\#}$, $\Delta H^{\#}$ and $\Delta S^{\#}$ are given at decomposition temperature of drugs

$$A \exp \frac{-E}{RT} = \upsilon \exp \frac{-\Delta G^{\#}}{RT} \quad (2)$$

$$\Delta H^{\#} = E - RT \quad (3)$$

$$\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#} \quad (4)$$

where, $\Delta G^{\#}$, $\Delta H^{\#}$, and $\Delta S^{\#}$ are free energy, enthalpy, and entropy of the activation, receptivity. υ is the $\upsilon = K_B T/h$ (where K_B and h are Boltzmann and Plank constant respectively). Table 3 gives the computed thermodynamic parameters for both the compounds studied.

Reaction rate constant determination

Assuming a first-order decomposition, the rate constant (k) for decomposition reaction could be calculated by the following equation [30]:

$$\log k = \log Z - E_a/2.3RT$$

which is for the temperature of 25 °C, and using activation energies (E_a) and frequency factors (Z) obtained in the above, the equation was solved for k. Table 3 listed the log k for each compound. By considering reaction rate constant calculated for naproxen using kinetic parameters obtained by different methods, naproxen reaction rate constant was compared with celecoxib reaction rate constant. It was found that the reaction rate constant of naproxen is lower than that calculated for the celecoxib.

Comparison of thermal behaviors of drug samples

In this study, the thermal behavior of two drug samples belonging to nonsteroidal anti-inflammatory drugs (NSAIDs) group was studied in identical conditions. For naproxen, as seen in Fig. 1; Table 1, melting phenomena occurred at about 7 °C lower than celecoxib sample. Also, for naproxen sample, the decomposition happened at about 60 °C lower than celecoxib. These results show that celecoxib with higher molecular weight is more stable than the naproxen. A comparison of decomposition temperature of these samples is shown in Table 1.

The values of the kinetic parameters that were obtained by the ASTM and Ozawa methods for these samples confirm the higher thermal stability of celecoxib in comparison with naproxen. The values of kinetic parameters (activation energy and frequency factor) of celecoxib are about 1.5 times higher than those values for naproxen. On the other hand, from the data presented in Table 3, it was found that the ratio of decomposition rate constant for naproxen to celecoxib is about 2×10^5 and hence, rate of decomposition for naproxen is considerably higher than celecoxib. These results show that naproxen in comparison with celecoxib is a heat-sensitive drug and needs more care during storage period.

On the other hand, the values of the kinetic parameters obtained for the studied NSAIDs samples in this study was compared to the results obtained for ibuprofen as another member of NSAIDs group [31]. This comparison showed that the value of activation energy (for zero-order reaction of vaporization) of ibuprofen (82–87 kJ mol^{-1}) is similar to the activation energy of decomposition for naproxen and about 1.5 times lower than this value for celecoxib. These results show that thermal stability of ibuprofen as anti-inflammatory drug is comparable to the thermal stability of naproxen. However, ibuprofen in comparison with celecoxib is a heat-sensitive drug and has a shorter shelf life.

Conclusions

The thermal stability of the two drug samples was determined by differential scanning calorimetry (DSC) and simultaneous thermogravimetry and differential thermal analysis (TG/DTA). Also, the influence of the different heating rates on the DSC behavior of the compounds was verified. Activation energies and frequency factors for the decomposition were calculated by different methods. According to the TG/DTA data, it was verified that the thermal decomposition of naproxen started after its melting point at approximately 196 °C. However, celecoxib was decomposed at about 352 °C, after its melting at temperature of 165 °C.

The values of the kinetic parameters that were obtained by the ASTM and Ozawa methods for naproxen and celecoxib showed good correlation, but the values obtained by the Ozawa method were slightly higher compared to those obtained by the ASTM method. On the other hand, the values of $\Delta S^{\#}$, $\Delta G^{\#}$, and $\Delta H^{\#}$ of the decomposition reaction of drugs were computed. Our finding showed that, the values of the $\Delta G^{\#}$ for the decomposition of naproxen and celecoxib are comparable. However, the values of the activation enthalpies ($\Delta H^{\#}$) and activation entropies ($\Delta S^{\#}$) for the decomposition of celecoxib are considerably higher than naproxen.

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