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Thermal behavior study and decomposition kinetics of amisulpride under non-isothermal and isothermal conditions

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Abstract The thermal decomposition of amisulpride was studied by simultaneous thermogravimetry/derivative thermogravimetry (TG/DTG), differential thermal analysis (DTA) and differential scanning calorimetry (DSC). The influence of the heating rate (5, 10, 15 and 20 °C min^{-1}) on the TG was verified. For the determination of kinetic parameters from the TG/DTG curves, the following methods were utilized: Arrhenius equation, Coats–Redfern, Horowitz–Metzger, Flynn–Wall–Ozawa and Starink methods. The activation energy obtained was found to be about 108 kJ mol^{-1}. Drug purity and melting point were determined by Van't Hoff equation. The results were in agreement with the recommended pharmacopoeia.

Keywords Amisulpride · Kinetic parameters · Isothermal · Non-isothermal · TG/DTA/DSC

Introduction

Amisulpride (AMS) is 4-amino-*N*-{[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl}-5(ethyl sulfonyl)-2-methoxybenzamide (Fig. 1). AMS is an atypical antipsychotic drug with benzamidic structure that is active against both positive (hallucinations, delusions) and negative (anergia, flat affectivity) symptoms of schizophrenia [1, 2]. Its pharmacological activity is based on the selective binding to D_2 and D_3 dopaminergic receptors. It has a lower risk of extra pyramidal side effects, and it is relatively better tolerated than conventional antipsychotic drugs.

Thermal analytical techniques can provide important data regarding storage and stability of drugs [3, 4]. The most widely used thermal analysis techniques are thermogravimetry/derivative thermogravimetry (TG/DTG), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) [5, 6]. These techniques are widely used in the pharmaceutical sciences for the characterization of solid drugs and excipients. 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, crystallization or gel-to-liquid crystal transition [7–9].

The thermal decomposition of drugs is interesting to predict the degradation rates at marketing 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 [10, 11]. Solid-state kinetic studies have increasing importance in thermal analysis, in which the main purposes are to calculate the parameters of the Arrhenius equation and to determine the mechanism(s) of pyrolysis reaction. These data can provide valuable information about time and conditions of storage [12, 13]. The knowledge of such parameters for pure drugs and for drug–excipient mixtures is also meaningful to elucidate miscibility/incompatibility and its effects on thermal stability.

In this work, thermal behavior of AMS was investigated by means of isothermal, non-isothermal conditions and DSC. The results allowed us to gain knowledge concerning this compound in the solid-state, including their thermal stability and thermal decomposition. Also, this study seeks

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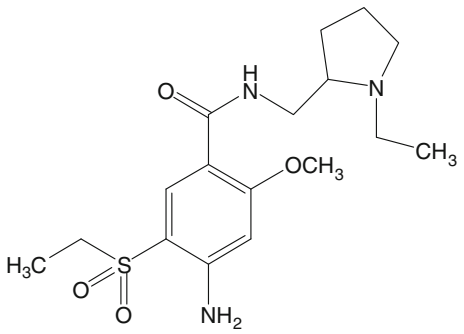


Fig. 1 Amisulpride

for determination of activation energy and kinetic parameters of the drug.

The thermoanalytical techniques cannot replace the classical stability studies that usually require weeks or months, but it can provide an early idea to direct the process toward the most successful formulation [14–16]. Furthermore, to the best of our knowledge, there is no report on the thermal behavior and decomposition kinetic of this drug.

Experimental

Materials

Amisulpride was kindly supplied from Sigma Pharmaceutical Industry, Egyptian Co., and its purity was found to be 99.50 %.

Methods

Thermogravimetry and differential thermal analysis were carried out using simultaneous Shimadzu thermogravimetric analyzer TGA-60 H with TA 60 software in dry nitrogen atmosphere at a flow rate of 30 mL min^{-1} in platinum crucible. The experiments were performed from room temperature up to 800 °C at different heating rates (5, 10, 15 and 20 °C min^{-1}). The sample mass was about 5 mg of the drug without any further treatment. The kinetic parameters of decomposition such as activation energy (E_a), frequency factor (A) and reaction order (n) were calculated from TG/DTG curves.

In the isothermal condition, the temperatures were 120, 130, 140 and 150 °C, with 10 °C temperature increments, under dynamic nitrogen atmosphere with the flow rate of 30 mL min^{-1}. The isothermal holding was monitored based on the time to a mass loss of 5 % decomposition.

The instrument was calibrated at each heating rate considered using a dedicated aluminum oxide standard in a platinum crucible.

The kinetic parameter and the order of reaction for Ozawa's method were obtained with TA 60 software.

DSC curve of AMS drug substance was recorded using Shimadzu DSC-50, in dynamic nitrogen atmosphere with a constant flow of 30 mL min^{-1}, and heating rate of 10 °C min^{-1}. The sample with a mass of about 5 mg was packed in platinum pan. DSC equipment was preliminarily calibrated with standard reference of indium (99.9 %). The purity determination was performed using heating rate of 10 °C min^{-1} in the temperature range from 25 to 190 °C in nitrogen atmosphere.

Results and discussion

Thermal behavior of amisulpride

The thermoanalytical graphs of AMS are presented in Fig. 2. The TG/DTA graphs obtained in nitrogen atmosphere showed that AMS decomposes during two steps. The first step shows a mass loss ($\Delta m = 57.62$ %) in the interval of 202–390 °C, suggesting the release of $C_9H_{12}SO_3N$ molecule (57.92 %, calc.). The second decomposition step shows a mass loss ($\Delta m = 42.38$ %) in the temperature range 393.41–726.86 °C, suggesting the loss of $C_6H_{12}N$ and CH_3NO, with an estimated mass loss of $\Delta m = 42.38$ % (42.08 %, calc.). The results are presented in Table 1. The DTA curve showed two thermal events during this temperature range: The first is an endothermic peak at 127 °C that is due to the melting of the compound (official mp 126–127 °C) [17]. The endothermic peak at 248 °C is attributed to the first decomposition corresponding to the first mass loss observed in TG/DTG thermogram curves as shown in Fig. 2. The sharp exothermic peak at 587 °C is due to the pyrolysis of the compound. The suggested pathway of thermal decomposition of AMS is shown Scheme 1.

Effect of heating rate

Table 1 shows the DTA data for the decomposition of AMS at several heating rates. It was found that by increasing the heating rate, the melting peaks and the decomposition temperature of the drugs were shifted to higher temperatures.

Kinetic methods

In the present investigation, the kinetic parameters such as activation energy and frequency factor of AMS were obtained from the TG/DTG data by non-isothermal methods proposed by Arrhenius equation [18–20], Coats–

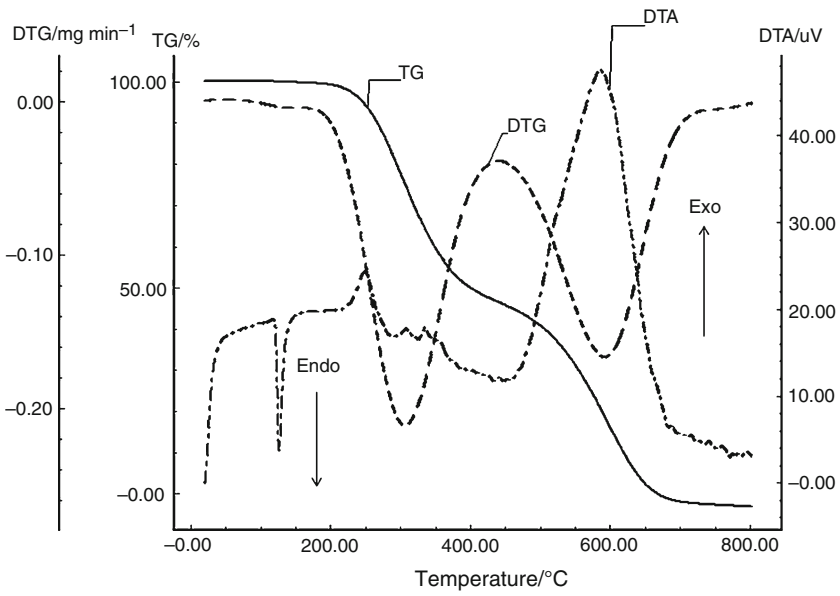
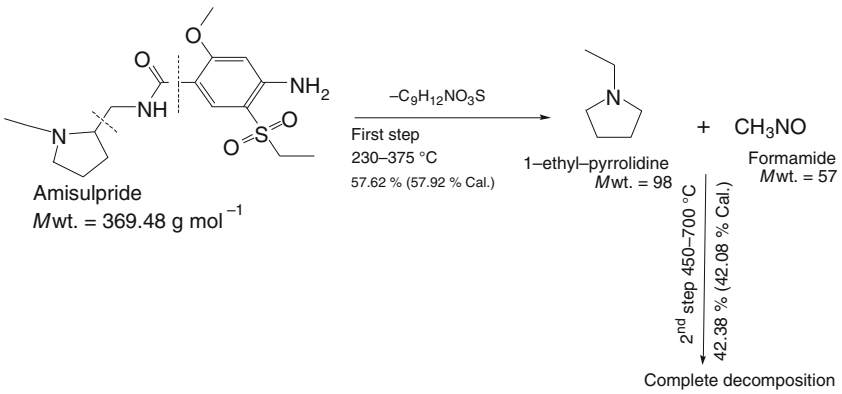


Fig. 2 TG/DTG and DTA curves of AMS in dynamic nitrogen atmosphere (30 mL min^{-1}) and heating rate 10 °C min^{-1}

Table 1 Thermoanalytical data of active substance at different heating rates

TG and DTG			DTA	
Heat flow/°C min^{-1}	Decomposition temperature/°C		Endothermic peaks/°C	Exothermic peaks/°C
	First step	Second step		
5	293	590	124	234,557
10	303	600	127	248,587
15	312	620	130	258,609
20	323	648	133	265,623



Scheme 1 Suggested thermal decomposition of AMS

Redfern (CR) [21], Horowitz–Metzger (HM) [22], Flynn–Wall–Ozawa (F–W–O) [23] and Starink methods [24, 25].

The kinetics of the main thermal decomposition step of AMS was studied using Arrhenius equation. Computation of the kinetic parameters was based on the use of the Arrhenius equation [18–20] applied to the solid-state reactions. A plot of ln $[(d\alpha/dt)/f(\alpha)]$ versus $1/T$ is constructed, where (α) is the conversion fraction $(d\alpha/dt)$ is the rate of the reaction, and $f(\alpha) =$ is a function of conversion.

The activation energy and the pre-exponential terms were calculated from the slope and the intercept, respectively. In addition, Coats–Redfern method can be used to

determine the kinetic parameters [21], namely $f(\alpha)$ functions, it can be expressed by the following:

$$\ln\frac{f(\alpha)}{T^2} = \ln\left[\frac{AR}{\beta E}\left(1-\frac{2RT}{E_a}\right)\right] - \frac{E_a}{RT} \quad (1)$$

where A is the pre-exponential factor. Based on Eq. (1), the activation energies and the pre-exponential factors for every $f(\alpha)$ function can be calculated from the slopes and the intercepts of the plots of $\ln(f(\alpha)/T^2)$ versus $1/T$ through a least-squares linear regression method. The pre-exponential factor A (min^{-1}) value was calculated from the intercept. The entropy of activation, ΔS^* in (kJ mol^{-1}) was calculated using the equation:

$$\Delta S^* = R[\ln(Ah/kT)] \quad (2)$$

where k is the Boltzmann constant, h is Planck's constant, and T_s is the DTG peak temperature.

The Horowitz–Metzger equation [Eq. (3)] is given in the following form:

$$\log\left[\log\frac{W_f}{W_f - W}\right] = \frac{\theta \cdot E_a}{2.303RT_s^2} - \log 2.303 \quad (3)$$

where W_f is the mass loss at the completion of the decomposition reaction, W is the mass loss up to temperature T, R is the gas constant, T_s is the DTG peak temperature, and $\theta = T - T_s$. A plot of log [log $W_f/(W_f - W)$] against θ would give a straight line, and E_a could be calculated from the slope.

The pre-exponential factor, A, was calculated from the following equation:

$$E_a/RT_s^2 = A/[\beta \exp(-E_a/RT_s)] \quad (4)$$

From the TG curves, the activation energy, E_a, the entropy of activation, ΔS^*, the enthalpy of activation, ΔH^*, and the Gibbs free energy, ΔG^*, were calculated, Table 2. The evaluated kinetic parameters for the first stages based on the Coats–Redfern and Horowitz–Metzger equations are listed in Table 2.

According to OZAWA [23, 25], 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.

To study the thermal decomposition kinetics for non-isothermal TG of AMS, the Ozawa's method available in the software of the thermal analysis system TA 60-WS (Shimadzu) was applied. In this study, four TG curves were obtained at different heating rates (β) of 5, 10, 15 and 20 °C min^{-1} (Fig. 3).

Ozawa's method was applied to data obtained from the four TG curves to determine the kinetics parameters including E_a at the beginning of the first event of mass loss, corresponding to the process of first thermal decomposition step (Table 2).

The order of reaction and the activation energy (E_a) of process were determined by Ozawa's plots in which slope of log heating rate versus $1/T$ was found to be first order.

The plot of ln β versus $1/T$ should give a straight line with a slope of $-E_a/R$ (Fig. 3). Meanwhile, the values of activation energy (E_a) for the AMS were also calculated by Starink method [24, 25] for comparison. In the Starink method, activation energy could be computed from the slope of the linear plot of ln $(\beta \cdot T_m^{-1.92})$ versus inverse of the maximum peak temperature ($1/T_m$), via Eq. (5). In this method, the activation energy could be obtained without requirement to the precise knowledge about the mechanism of decomposition reaction using the following equation:

$$\ln \beta \cdot T_m^{-1.92} + 1.0008\, E_a/RT_m = C \quad (5)$$

In Eq. (5), again T_m (K) is maximum peak temperature of DTG curves at various heating rates (β/K min^{-1}). The plots of ln $(\beta \cdot T_m^{-1.92})$ versus the inverse of maximum temperatures of DTG peaks ($1/T_m$) show straight lines, which confirms no variation in the mechanism of thermal decomposition reaction of drug over the temperature range studied [26]. The Arrhenius factor (A) was also evaluated from the following equation:

$$A = \beta(E_a/RT^2)\exp(E_a/RT) \quad (6)$$

The values of the activation energy (E_a) obtained by the five methods are in good agreement (Table 2).

The calculated kinetic parameters for AMS are also included in Table 2. A comparison between the results obtained by applying different kinetic methods revealed that the values of activation energies calculated for AMS are very close to each other. The obtained kinetic

Table 2 Comparison of kinetic parameters of the drug sample obtained by different methods

Parameters	Arrhenius	CR	HM	F–W–O	Starink
E_a/kJ mol^{-1}	108.91	108.26	108.31	108.00	108.10
A/min^{-1}	2.85×10^9	2.47×10^9	2.50×10^9	2.34×10^9	2.39×10^9
ΔS^*/kJ mol^{-1}	−70.01	−70.59	−70.50	−71.06	−70.88
ΔH^*/kJ mol^{-1}	104.11	103.46	103.51	103.20	103.30
ΔG^*/kJ mol^{-1}	144.16	144.19	144.19	144.20	122.20

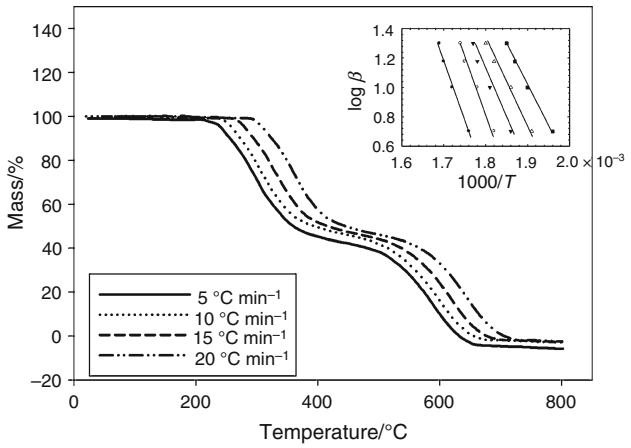


Fig. 3 TG curves of AMS standard at 5, 10, 15 and 20 °C min^{-1} (*inset* shows Ozawa's plot)

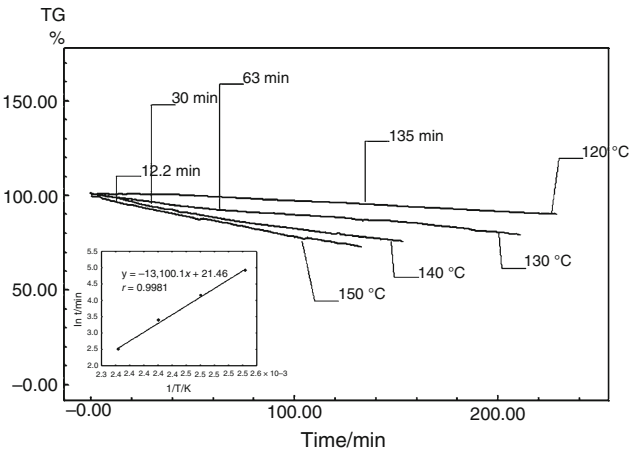


Fig. 4 Isothermal TG curves AMS-active substance at 120, 130, 140 and 150 °C (*inset* shows plot of ln *t* versus 1/*T* for AMS standard using Arrhenius equation)

parameters were used to evaluate the thermodynamic parameters of activation, including change in entropy (ΔS^*), enthalpy (ΔH^*) and free energy (ΔG^*) corresponding to the activation by using previously mentioned equations.

The values of the activation energy (E_a) obtained by the five methods are in good agreement. The values of E_a showed a considerable thermal stability of the AMS-active substance, considering that 65 % of the values of E_a found in the literature are in 100–230 kJ mol^{-1} range [27].

The isothermal TG curves superimposed of AMS are illustrated in Fig. 4 and were recorded at 120, 130, 140 and 150 °C. These curves show mass loss rate dependence in temperature function of isothermal, the higher the temperature, the lower the necessary time, so the same mass loss occur. The curves were used to obtain the graphic of ln *t* versus 1/*T* (K^{-1}) at a constant conversion level 0.5. From this linear regression method, the equation for the

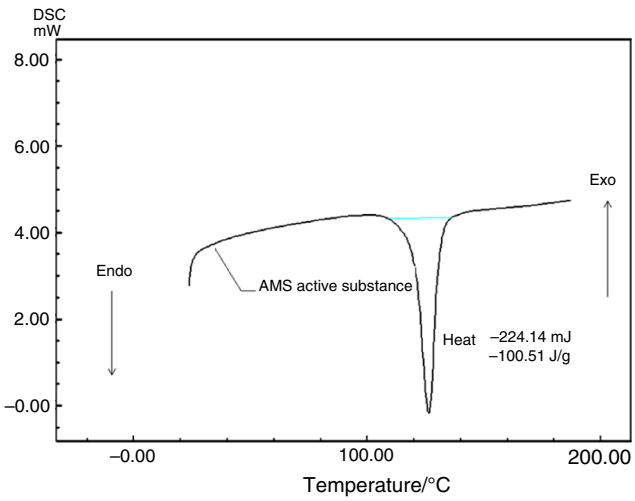


Fig. 5 DSC curves of AMS-active substance obtained in dynamic nitrogen atmosphere (30 mL min^{-1}) and heating rate 10 °C min^{-1}

line is $y = -13{,}100.1x + 21.46$ and $r = 0.9981$ are obtained. The value of the activation energy can be calculated from the slope with the molar gas constant ($R = 8.314$). The calculated activation energy was found to be 108.91 kJ mol^{-1}. This result is in agreement with the values obtained from the dynamic methods, and this is an important experimental finding (Fig. 4).

The DSC purity method can be used typically in the case of high-purity (>99 %) crystalline substances. This purity analysis is based on the phenomenon that in eutectic systems, the melting points of crystalline substances decrease under the influence of the chemical impurity [28]. The thermodynamic relationships are described by the simplified Van't Hoff law.

$$T_s = T_o - \frac{RT_o^2 X_2}{\Delta H_f \cdot F} \tag{7}$$

where T_s is the sample peak at temperature (K), T_o is the melting point of pure component (K), R is the gas constant, X is the concentration of impurity (grams fraction), ΔH_f = heat of fusion of pure component (J mg^{-1}), and F is the fraction of sample melted at T_s (Fig. 5). The amount of the impurities can be calculated from the shape of the curve after certain thermodynamic considerations and with certain arithmetical simplifications of the Van't Hoff law [29]. Purity determination is officially listed in the US Pharmacopoeias in general chapter on thermal analysis [30–36].

The results obtained by the official and reported methods afforded values similar to those found by DSC (126.8 °C). Comparison of the data on the studied drug revealed the importance of the DSC technique for quality control of bioactive drugs. This justifies the use of DSC as a routine technique for identification of drugs designed for pharmaceutical use, through the melting point.

Conclusions

A kinetic study was performed for the thermal decomposition of AMS-active substance, in a nitrogen atmosphere under non-isothermal conditions, comparatively with the study performed in isothermal conditions. The study suggests that AMS decomposes in two steps. The values of the activation energy and the pre-exponential factor, determined with different methods, are in fairly good agreement. They are situated in a narrow range (E_a = 108–108.91 kJ mol^{-1}, $A = 1.53 \times 10^9$–1.97×10^9 min^{-1}). This fact indicates the correctness of the applied methods. The E_a together with the melting point, which characterizes the purity of substances, can be used in the pre-formulation and production steps of drugs.

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