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Research Article

Thermal Stability and Decomposition Kinetic Studies of Acyclovir and Zidovudine Drug Compounds

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Abstract. Investigations on thermal behavior of drug samples such as acyclovir and zidovudine are interesting not only for obtaining stability information for their processing in pharmaceutical industry but also for predicting their shelf lives and suitable storage conditions. The present work describes thermal behaviors and decomposition kinetics of acyclovir and zidovudine in solid state, studied by some thermal analysis techniques including differential scanning calorimetry (DSC) and simultaneous thermogravimetry–differential thermal analysis (TG/DTA). TG analysis revealed that thermal degradation of the acyclovir and zidovudine is started at the temperatures of 400°C and 190°C, respectively. Meanwhile, TG–DTA analysis of acyclovir indicated that this drug melts at about 256°C. However, melting of zidovudine occurred at 142°C, which is 100°C before starting its decomposition (242°C). Different heating rates were applied to study the DSC behavior of drug samples in order to compute their thermokinetic and thermodynamic parameters by non-isothermal kinetic methods. Thermokinetic data showed that both drugs at the room temperature have slow degradation reaction rates and long shelf lives. However, acyclovir is considerably more thermally stable than zidovudine.

KEY WORDS: acyclovir; decomposition kinetics; drug compound; thermal stability; zidovudine.

INTRODUCTION

Acyclovir as a drug is an acyclic guanine nucleoside analogue with IUPAC name of 2-amino-9-(2-hydroxyethoxymethyl)-3H-purin-6-one. This compound is widely used in clinics as an anti-herpetic agent. The main disadvantage of this drug is its limited absorption after oral administration in humans which caused the research for prodrugs (1,2). The structure of Acyclovir, commonly prescribed as Zovirax, is shown in Scheme 1.

Azidothymidine (with commercial name of Zidovudine or AZT) is the first drug which has been approved by the Food and Drug Administration (USA) for the treatment of human immunodeficiency virus (HIV) infection and prevention of mother-to-child transmission of HIV. Zidovudine is classified as a nucleoside reverse transcriptase inhibitor. This compound is used in combination with some anti-virus medicines in the treatment of infection due to HIV. Zidovudine is used to reduce the speed of disease progression in patients infected by HIV with advanced, early, or no symptoms. This compound is also useful for preventing the virus passing in pregnant women, infected by HIV, to their babies during pregnancy and at birth (3–5). Scheme 2 shows the chemical structure of AZT.

Thermal analysis techniques such as differential scanning calorimetry (DSC), differential thermal analysis (DTA), and thermogravimetry (TG) have been known methods in the physicochemical characterization of different materials since several years ago (6–9). Thermal analysis techniques are widely used in the pre-formulation studies and development of drugs and substances of pharmacological interest (10–13). Thermal analysis methods are described as general techniques in the pharmacopoeia, but description of their uses is limited to only a few monographs for determination of purity, the loss on drying of reference substances, studies of polymorphs, solvates and hydrates, melting-point determination, and quantification of volatile components in drugs (10,14–16).

Thermokinetic data corresponding to the decomposition reaction could be calculated by thermal analysis results, which makes possible the determination of some valuable parameters on thermal behavior of drugs and medicine compounds such as decomposition rates, possible mechanisms, and values of some thermokinetic and thermodynamic parameters (17). The thermodynamic parameters corresponding to the activation of thermal decomposition reaction of drugs in solid state are useful in obtaining knowledge about drug decomposition reactions. The value of Gibbs energy ($\Delta G^{\#}$) reflects total enhancement of energy in the activated complex system as the intermediate of drug consumption and the decomposition

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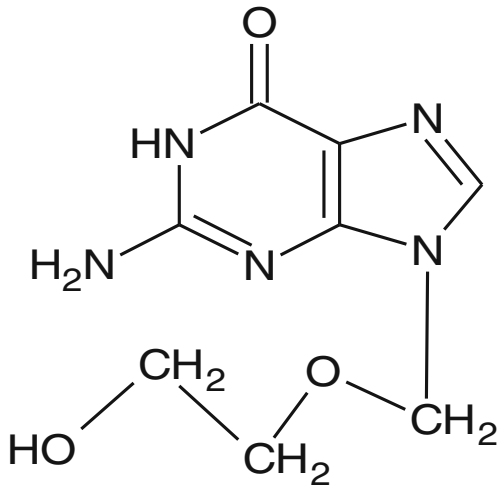
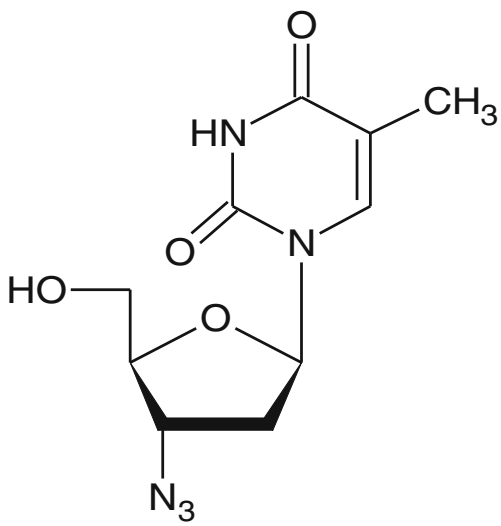


Scheme 1. Chemical structure of acyclovir

products formation. The Gibbs energy is influenced by two other thermodynamic parameters, namely, enthalpy ($\Delta H^{\#}$) and entropy ($\Delta S^{\#}$) of the activated complex formation. The value of activation enthalpy shows the energy differences between the activated complex and initial drug structure. Small quantity for this parameter is in favor of formation of the activated complex due to the potential energy barrier. Meanwhile, the value of activation entropy indicates the situation of the system in its own thermodynamic equilibrium. The low values of activation entropy reveal that the reagent has a low reactivity and the required time to form the activated complex is long. However, high values for activation entropy confirm that the reagent is far from its own thermodynamic equilibrium; therefore, the reactivity of the compound is high, and the system can react faster to form the activated complex, and hence, gives shorter reaction times. Furthermore, prediction of the shelf life (i.e., the maximum length of time that the drug preserves its activity) or half-life (i.e., length of required time for isothermal decomposition the half of compound) at a given temperature is possible *via* heating the sample and facilitating its decomposition process by the aid of thermal analysis techniques (18–24).



Scheme 2. Chemical structure of zidovudine

Since acyclovir and zidovudine have widespread applications in medicine and drug industry, many papers could be found about the pharmaceutical properties, analysis, and determination of these drugs (25–31). However, to the best our knowledge, only few data are available on the thermal decomposition and degradation behavior of zidovudine (32,33), and there is no report on its decomposition thermokinetic data, while there is no report available on the thermal behavior and degradation kinetic of acyclovir. The main goal of this work was to investigate the thermokinetic and thermodynamic parameters corresponding to decomposition processes of the two drugs by means of thermal analysis techniques including DSC and TG/DTA. Thermal analysis results allowed us to obtain essential information concerning these drugs in the solid state, including their thermal behavior and thermal decomposition reaction. Also, in this study, the thermokinetic and thermodynamic parameters of the drugs were determined under non-isothermal conditions.

EXPERIMENTAL

Pharmaceutical grade acyclovir and zidovudine powders (min. 99.5%, Bakhtar Bioshimi, Kermanshah, Iran) were used without further purification. The DSC curves were obtained by a Du Pont differential scanning calorimeter model DSC 910S, at a temperature range of 50–700°C using an alumina crucible, at different heating rates (i.e., 5, 10, 15, and 20°Cmin^{-1}), under nitrogen atmosphere with a flow rate of 50 $\text{ml}\,\text{min}^{-1}$.

Simultaneous thermal analysis (TG) and differential thermal analysis (DTA) studies were performed by a Stanton Redcroft, STA-780 series with an alumina crucible, at an applying heating rate of 10°Cmin^{-1} over a temperature range of 50–800°C, under nitrogen atmosphere with the flow rate of 50 $\text{ml}\,\text{min}^{-1}$. The used drug sample mass was 3.0 mg.

RESULTS AND DISCUSSION

Thermal Behavior of Drug Samples

The obtained thermoanalytical curves of acyclovir are shown in Fig. 1a. DTA curve shows an endothermic behavior commencing near 256°C, without any mass loss in TG curve, which is the melting point of acyclovir. Thus, acyclovir is thermally stable up to the melting point, and no thermal event was observed before the melting of drug. However, at higher temperatures, the acyclovir presents two significant thermal peaks in temperature range of 400°C to 560°C, for which, Δm=88% and T_{peak} of DTA=438.6°C and 520.4°C. By considering these results and chemical structure of this drug shown in Scheme 1, the first stage in thermal decomposition of the drug may correspond to cleavage followed by elimination of the alcoholic-etheric side chain from acyclovir structure and consequent formation of guamine as residual mass. In the second step of the decomposition process, the residue guamine is decomposed due to the further heating. However, TG/DTA curves over 520°C show no considerable thermal phenomenon.

The results of simultaneous TG/DTA corresponding to the zidovudine are shown in Fig. 1b. These curves exhibit an endothermic peak about 142.2°C without any change in the mass of sample corresponding to the melting of zidovudine. According to the TG/DTA data, a single-step mass loss of

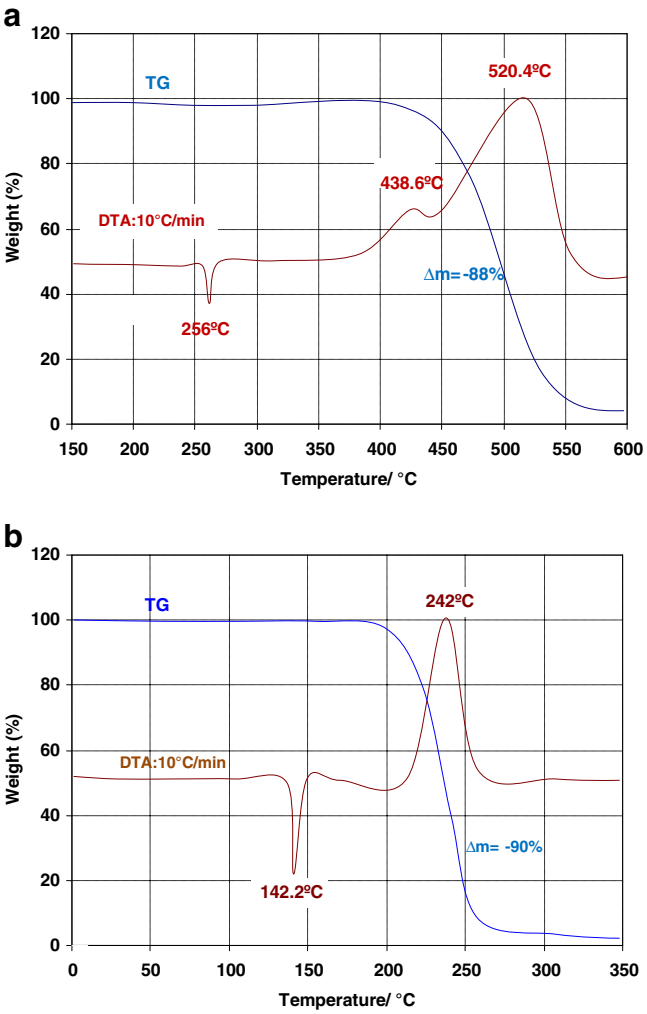


Fig. 1. TG/DTA curves for drug samples: acyclovir **a** and zidovudine **b**. Conditions: sample mass, 3.0 mg; heating rate, 10°C/min; nitrogen atmosphere

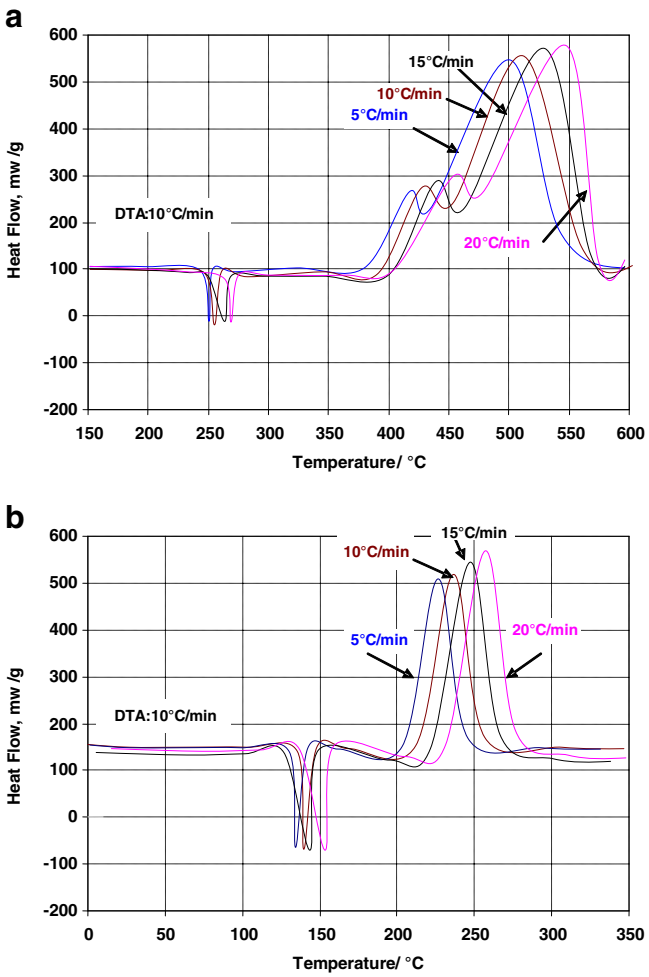


Fig. 2. Effect of heating rate on melting points and decomposition temperatures of acyclovir **a** and zidovudine **b**; Conditions: sample mass 3.0 mg; nitrogen atmosphere

Δm=90% occurred at 190–280°C. Based on the chemical structure of the drug shown in Scheme 2 and the observed thermal behavior for zidovudine, it could be proposed that the thermal decomposition of this drug is started by the cleavage followed by elimination of the azide group from the structure of zidovudine and hence formation of thymine, which is continued by thermal decomposition of the formed thymine (32). Up to the 300°C, decomposition process of drug became complete, and no further mass loss was observed above this temperature. Such thermal pattern reveals that decomposition reaction of the zidovudine is started at about 100°C above its melting. Table I summarizes the resulting thermal analysis data for both drugs obtained *via* TG/DTA studies.

Table I. TG/DTA Results for Studied Drug Samples

Drug	Transition temperature/°C			Mass loss/%
	Melting	Decomposition	ΔT[a]	Δm
Acyclovir	256.6	438.6, 520.4	400–560	88
Zidovudine	142.2	242.3	190–280	90

[a] ΔT: temperature range corresponds to fall in sample's mass

Effect of Heating Rate on DSC Curves and Thermokinetic Studies

Figure 2 shows the DSC curves for thermal decomposition of acyclovir and zidovudine at several heating rates. It was found that, increasing the heating rate shifts both the melting and decomposition peaks of acyclovir and zidovudine

Table II. Melting Points and Decomposition Temperatures for Acyclovir and Zidovudine Obtained by DSC at Various Heating Rates

Drug	Acyclovir			Zidovudine	
		Decomposition temperature (°C)			
Heat flow (°Cmin^{-1})	Melting point (°C)	First step	Second step	Melting point (°C)	Decomposition temperature (°C)
5	253.0	424.4	498.6	123.7	229.6
10	256.6	438.6	520.4	124.2	242.3
15	260.2	447.3	540.6	124.7	249.0
20	262.7	454.2	552.0	125.1	253.8

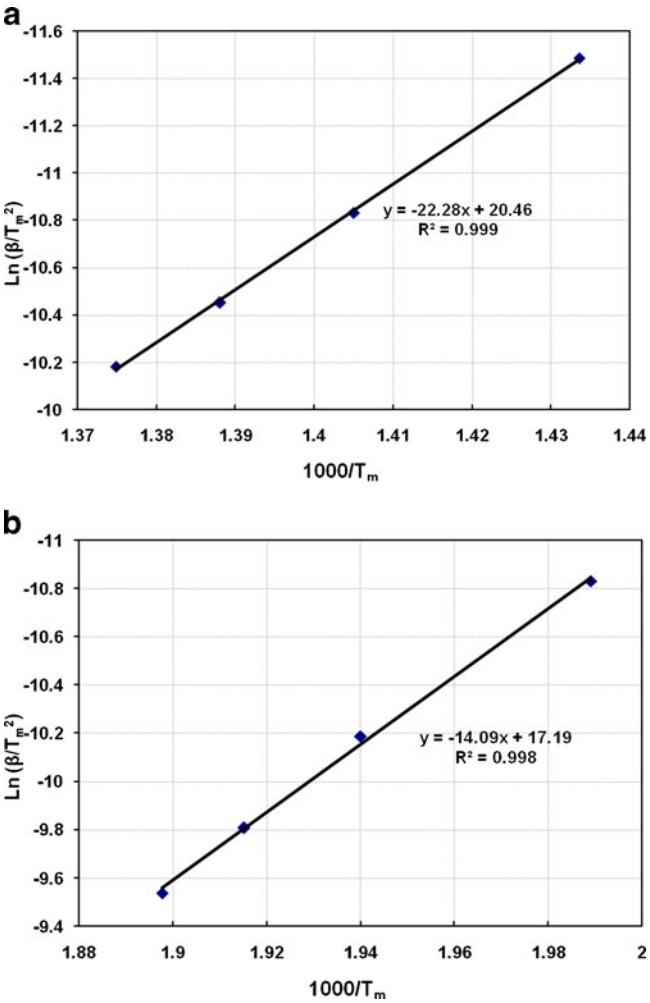


Fig. 3. Plots of $ln\ (\beta.T_m^{-2})$ *versus* $1/T_m$ for drug samples (β is heating rate in $K min^{-1}$ and T_m is maximum peak temperature in K): **a** acyclovir and **b** zidovudine

to higher temperatures. The observed variations in the peak temperatures of DSC curves can be used for the determination of thermokinetic parameters of the drug samples. The melting points and decomposition temperatures at different heating rates, evaluated from the corresponding DSC curves, for both drugs are summarized in Table II.

In the present investigation, two well-known methods including ASTM E698 (34,35) and Starink (36) were applied to the evaluation of the kinetic parameters of drug's decomposition reactions. The first method used for the calculation of the drugs kinetic parameters was ASTM method E698 (34). According to this method, the $ln\ (\beta.T_m^{-2})$ is plotted against $1/T_m$, where T_m (K) is the maximum peak temperatures of DSC curves obtained at various heating rates (β/Kmin^{-1}), and the activation energy (E_a) is then determined from the slope of the resulting linear plot. The calculations for both drugs were carried out using the T_m (K) values presented in Table II.

Figure 3 shows the resulting graph of $ln\ (\beta.T_m^{-2})$ *versus* $1/T_m$ for both acyclovir and zidovudine. As is obvious, the obtained graphs for both drugs are quite linear, indicating that the decomposition mechanism of the drugs was not changed under various heating rates (35). The corresponding activation energies (E_a) for decomposition of drugs were calculated from the slope of the linear graphs. Meanwhile, as proposed by ASTM E698, the values of Arrhenius factor, log A (s^{-1}), for drugs could be calculated from the following equation:

$$A = \beta(E_a/RT_m^2)\exp(E_a/RT_m) \quad (1)$$

The resulting activation energies and Arrhenius factors for acyclovir and zidovudine obtained by the ASTM method are given in Tables III and IV, respectively. Meanwhile, the values of activation energy (E_a) for the drugs were also calculated by Starink method (36) for comparison. In the Starink method, activation energy could be computed from the slope of the linear plot of $ln\ (\beta.T_m^{-1.92})$ *versus* inverse of the maximum peak temperature ($1/T_m$), *via* Eq. (2). In this method, the activation energy could be obtained without requirement to the precise knowledge about the mechanism of decomposition reaction.

$$\mathrm{Ln}(\beta/T_m^{1.92}) + 1.0008\ E_a/RT_m = C \quad (2)$$

In Eq. (2), again T_m (K) is maximum peak temperature of DSC curves at various heating rates (β/Kmin^{-1}). As shown in Fig. 4, the plots of $ln\ (\beta.T_m^{-1.92})$ *versus* the inverse of maximum temperatures of DSC peaks ($1/T_m$) show straight lines for both acyclovir and zidovudine, which confirm no variation in the mechanism of thermal decomposition reaction of drugs over the temperature range studied (35). The Arrhenius factor (A) for both drugs was also evaluated from Eq. (1). The calculated thermokinetic data for acyclovir and zidovudine are also included in Tables III and IV, respectively. A comparison between the results obtained by applying different kinetic methods (i.e., ASTM and Starink) revealed that the values of activation energies calculated for each drug sample are very close to each other. These obtained kinetic parameters were used to evaluate the thermodynamic parameters of activation for both drugs, including change

Table III. Comparison of Kinetic Parameters for the First Step of Acyclovir Decomposition Reaction Obtained by ASTM and Starink Methods

Kinetic method	Activation energy (KJ.mol^{-1})	Arrhenius factor Log A (s^{-1})	$\Delta G^{\#}$ (KJmol^{-1})	$\Delta H^{\#}$ (KJmol^{-1})	$\Delta S^{\#}$ (J$mol^{-1}K^{-1}$)	Rate constant k (s^{-1})
ASTM	185.3	13.24	184.3	179.3	−6.5	5.12×10^{-20}
Starink	185.6	13.26	184.3	179.7	−6.5	5.12×10^{-20}

Table IV. Comparison of Kinetic Parameters of Pure Zidovudine Obtained by ASTM and Starink Methods

Kinetic method	Activation energy ($KJmol^{-1}$)	Arrhenius factor Log A (s^{-1})	$\Delta G^{\#}$ ($KJmol^{-1}$)	$\Delta H^{\#}$ ($KJmol^{-1}$)	$\Delta S^{\#}$ ($KJmol^{-1}K^{-1}$)	Rate constant k (s^{-1})
ASTM	117.2	11.62	131.1	112.9	−35	1.14×10^{-9}
Starink	117.5	11.64	131.1	113.2	−35	1.10×10^{-9}

in entropy ($\Delta S^{\#}$), enthalpy ($\Delta H^{\#}$), and free energy ($\Delta G^{\#}$) corresponding to the activation by the following equations (37).

$$A \exp \frac{-E}{RT} = v \exp \frac{-\Delta G^{\neq}}{RT} \tag{3}$$

$$\Delta H^{\neq} = E - RT \tag{4}$$

$$\Delta G^{\neq} = \Delta H^{\neq} - T\,\Delta S^{\neq} \tag{5}$$

In Eq. (3), $v=k_B T/h$ (where k_B is Boltzmann constant and h is Plank constant). The resulting thermodynamic parameters of activation for the acyclovir and zidovudine are also included in Tables III and IV, respectively. Comparing the calculated values of thermodynamic parameters for drug samples revealed that $\Delta S^{\#}$ for zidovudine is considerably lower than that for acyclovir. This lower value of $\Delta S^{\#}$ for zidovudine confirms that its activated complex in decomposition process possesses a higher degree of arrangement (more entropy) than initial state of drug; however, this trend is reversed for acyclovir. Based on the activated complex (transition state) theory (38–40), higher value of $\Delta S^{\#}$ for acyclovir makes its thermal decomposition a slow reaction, while the zidovudine decomposes quickly. Meanwhile, the positive values of $\Delta H^{\#}$ and $\Delta G^{\#}$ for both drugs show that they are dependent on the heat introduced and possess non-spontaneous decomposition reactions. However, the value of $\Delta G^{\#}$ for acyclovir decomposition reaction is considerably higher than that for zidovudine. Also, the value of activation enthalpy ($\Delta H^{\#}$) for acyclovir decomposition is lower, in comparison with zidovudine.

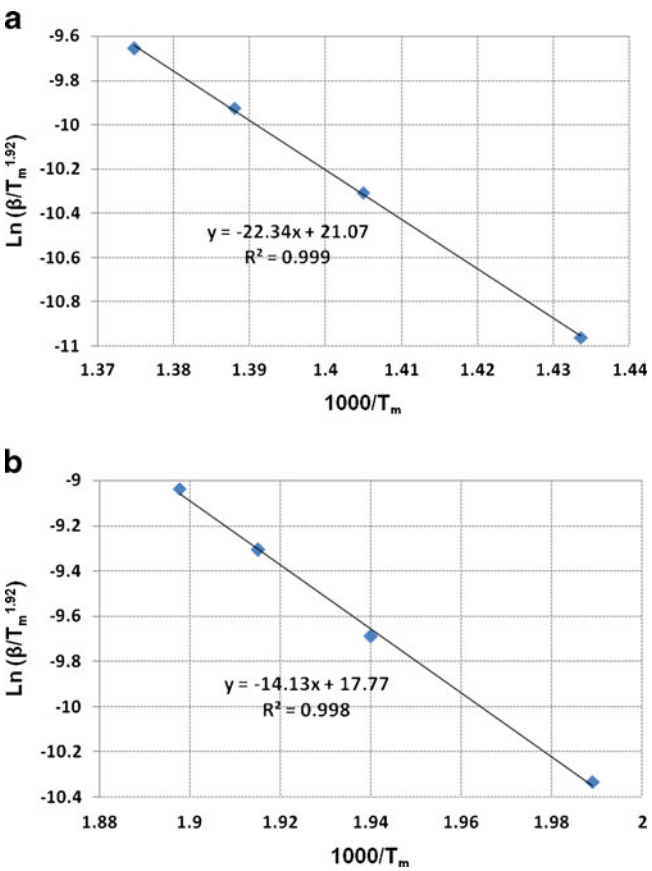


Fig. 4. Graph of ln ($\beta.T_m^{-1.92}$) *versus* $1/T_m$ for drug samples (β is heating rate in $K.min^{-1}$ and T_m is maximum peak temperature in K): **a** acyclovir and **b** zidovudine

Calculation of Reaction Rate Constant

The values of reaction rate constants (k) for thermal decomposition of drugs were calculated at the room temperature of 25°C using the following equation and the previously mentioned values for activation energies (E_a) and Arrhenius factors (A) for acyclovir and zidovudine (41):

$$\log k = \log A - E_a/2.3RT \tag{6}$$

The calculated k values for acyclovir and zidovudine are also presented in Tables III and IV, respectively. The results obtained for thermal decomposition kinetic and reaction rate constant of the pure acyclovir showed that this drug is extremely thermally stable and possess a long shelf life. Also, due to the high thermal stability of acyclovir, variation in

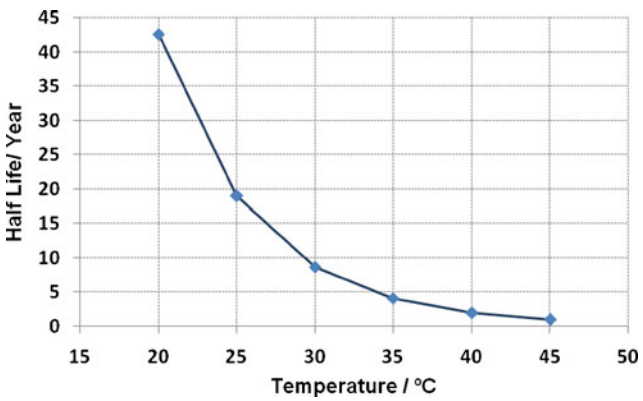


Fig. 5. Graphic for predicted half-life of zidovudine drug under various temperatures

storage temperature of the drug (from 20°C to 45°C) has a negligible effect on its shelf life (42). On the other hand, zidovudine possesses a lower thermal stability and lower activation energy for its solid-state thermal decomposition. Thus, as could be seen in Fig. 5, the predicted half-life for this drug considerably varies under different storage temperatures, and increasing the storage temperature for this drug reduces its half-life progressively. Thus, zidovudine could be introduced as a more heat-sensitive drug compared with acyclovir, which requires more care during storage. However, long time storage of both drugs in pure form under room temperature is possible. Meanwhile, it should be noted that the drugs may be incompatible with some excipients so that their shelf lives in pharmaceutical formulations will be shorter (42). Therefore, zidovudine as a heat-sensitive drug should be stored in pure form for long time storage, while acyclovir as a thermally stable drug may possess an acceptable shelf life in the presence of excipients and in pharmaceutical formulations.

CONCLUSION

Thermal behaviors of the acyclovir and zidovudine drug samples were investigated by thermal analysis techniques. TG/DTA results revealed that the thermal decomposition reaction for acyclovir is started more than 150°C after its melting point. However, zidovudine was thermally decomposed at about 100°C after its melting, at a temperature of 242°C. Meanwhile, thermokinetic and thermodynamic parameters corresponding to thermal decomposition reactions of drugs were predicted by the aid of DSC curves obtained at different heating rates. Two well-known kinetic methods (i.e., ASTM and Starink) were applied to calculate activation energy and Arrhenius factor for the drugs, and the results of both methods confirm each other well. Based on the results of degradation kinetics and predicted shelf lives, it could be concluded that acyclovir is an extremely thermally stable drug. However, zidovudine has lower stability and its shelf life is dependent on its storage temperature.

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