Estimation of Intramolecular Cyclization Activation Energies via Isothermal Gravimetric Analysis: A Technical Note

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INTRODUCTION

Intramolecular cyclization (Figure 1) is a commonly observed degradation pathway for many compounds, ie, quinapril, lisinopril, and aspartame.[1-7] The solid-state cyclization of these chemicals is interfused with solid-state form conversion such as crystalline to amorphous, hydrate to anhydrate, and salt to free form. The latter may also cause pH-related degradation. Depending on the experimental conditions, the degradation products can exist as solids, liquids, and gases or combined mixtures. These factors complicate the determination of intramolecular cyclization kinetic parameters.

Thermal analysis techniques such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) in corroboration with powder x-ray diffractometry (PXRD) and Fourier transform infrared microspectroscopy (FT-IR) are commonly used to deconvolute the intramolecular cyclization kinetic processes.[1-7] Among these analytical methods, TGA has been used to obtain the thermal stability parameters of solid chemicals.[8-11] These approaches are based on monitoring weight change as an indicator of solid-state conversion and may be performed under isothermal, nonisothermal, or modulated conditions.[12-14] The data generated from these experiments can be analyzed and manipulated by either model or model-free approaches to obtain Arrhenius kinetic parameters such as activation energy (E_a) and preexponential factor.[15,16]

For example, the model-free method is derived from a general expression of a solid-state reaction:

$$g(\alpha) = kt, \qquad (1)$$

where k is the specific rate constant, t is time, α is the degree of conversion and $g(\alpha)$ is the conversion function related to a solid-phase reaction mechanism, ie, diffusion, nuclei growth or phase boundary control.

The degree of conversion α (fraction of compound decomposed) at any given time is expressed as

$$\alpha_{(t)} = \frac{(m_i - m_t)}{(m_i - m_f)} , \qquad (2)$$

where m_i, m_t, and m_f are the masses at initial, at time t, and at final, respectively.

For estimating activation energy, the Arrhenius equation is commonly used:

$$ln\, k = ln\, A - \frac{E_a}{RT} , \qquad (3)$$

where A is the preexponential factor, E_a is the activation energy, T is the experimental temperature, and R is the universal gas constant.

By combining Equations 1 and 3, the isoconversional equation can be expressed as

$$g(\alpha) = A\, exp \left(\frac{-E_a}{RT} \right) t_\alpha , \qquad (4)$$

where t_α is the time at any given degree of conversion, which is known from the TGA data. Taking the natural log of Equation 4 and rearranging gives the following:

$$-ln\, t_\alpha = ln\, \frac{A_\alpha}{g(\alpha)} - \frac{E_a}{RT} . \qquad (5)$$

By plotting $-ln\, t_\alpha$ versus $1/T$, the activation energy may be found at any given α value from the slope of the regression line. As can be seen from Equation 5, the activation energy is not dependent on the degradation model, ie, diffusion, nuclei growth, or phase boundary control, whereas model-fitting methods can be misleading for estimating Arrhenius parameters. Therefore, it has suggested that the model-free method gives a better estimation of E_a.[15-17]

The goal of this study was to use the model-free kinetic approach to obtain the activation energies of 4 exploratory compounds and further rank their relative solid-state thermal stability based on their activation energy values. The

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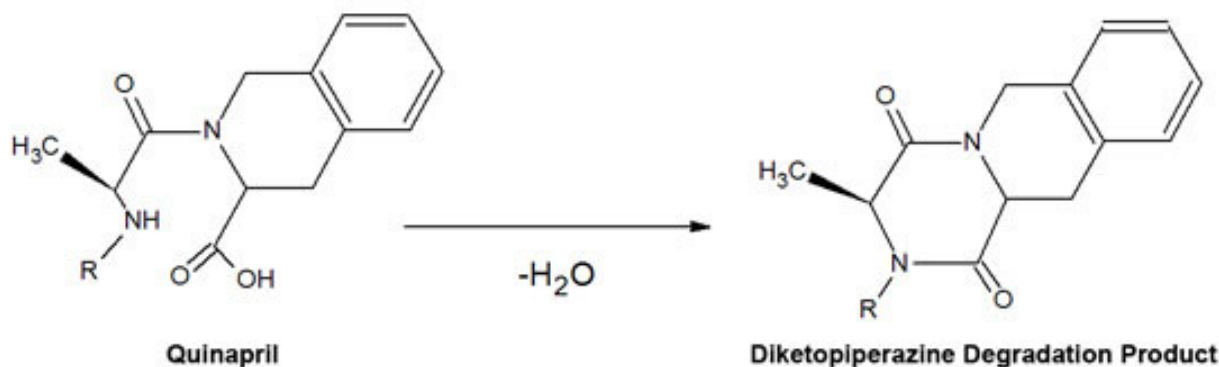
Figure 1. Intramolecular cyclization of quinapril.[1]

compounds investigated undergo the intramolecular cyclization process similar to that of quinapril and aspartame and form gaseous impurities at elevated temperatures. However, unlike quinapril and aspartame, the compounds investigated in this report are anhydrous, crystalline free-forms with fairly simple chemical structures. All these features suggest a less complicated solid-state conversion and make thermal analysis a suitable tool to estimate thermal kinetic parameters.

MATERIALS AND METHODS

Materials

The key physicochemical parameters of the compounds tested in this report are listed in Table 1. All samples were obtained from Pharmacy Operation, Pfizer (Ann Arbor, MI) and used as received.

Specific Surface Area Measurement

The specific surface area (SSA, m^2/g) determinations were conducted using a Micromeritics Gemini surface area analyzer (Micromeritics Instruments Inc, Norcross, GA) with liquid nitrogen as the coolant. Prior to adsorption measurements, the samples (~1 g) were outgassed at 25ºC under a nitrogen purge using a Micromeritics FlowPrep 060 (Micromeritics Instruments Inc). The SSA was calculated using the Brunauer-Emmett-Teller (BET) theory applied to nitrogen adsorption measurements over a P/Po range of 0.05 to 0.25.

Thermogravimetric Analysis

A TGA Q500 (TA Instruments, New Castle, DE) was used for isothermal gravimetric analysis. Approximately 10 mg of sample was placed into an aluminum sample pan (ID 20 mm) and held isothermally at predetermined temperatures under a purge of nitrogen at a flow rate of 60 mL/min.

RESULTS AND DISCUSSION

The SSA from each sample set and their corresponding TGA run times are summarized in Table 2. Because of the small particle size, only the bulk powder of compound A was tested. Compound A had the highest SSA that was 2- to 10-fold higher than other compounds. Depending on the temperature setting, the time for completion of 1 TGA assay ranged from 60 to 4000 minutes. In this investigation, compound D had the longest experimental run time ranging from 450 to 4000 minutes which equaled about ~7.5 days to complete a sample set.

For the TGA experiment, the isothermal temperatures were set at ~15ºC below the melting point of the compounds tested to prevent melting of sample, which could further complicate interpretation of the thermal analysis results. Figure 2 displays the fraction of conversion (α)-time profiles for the large particle of compound D under different isothermal conditions. While the α-time profiles for compounds A, B, and C are not displayed, they showed the similar profiles to that of compound D but with shorter completion times.

Table 1. Key Physicochemical Parameters of Compounds Tested

Compounds	A	B	C*	D
Molecular weight	187	185	171	161
Melting point, ºC	181	187	178	178
Crystal shape	Needle	Hexagonal plate	Rectangular prism	Cube
Experimental temp, ºC	140-160	145-165	135-155	145-165

*Sample has been pre-milled.

**Table 2.** Thermogravimetric Analysis (TGA) Run Time and Specific Surfac Area (SSA) for Compounds Tested

Compounds	A	B		C		D	
Particle size*	Bulk	L	S	L	S	L	S
SSA (m^2/g)	1.24	0.10	0.37	0.14	0.57	0.10	0.25
TGA time (min)	60-600	300-2400		60-800		450-4000	

*Bulk particle with D_{50} = 32 μm; L = 180-250 μm; S < 90 μm. D_{50} indicates median of the particle size distribution; L, large particles; S, small particles.

As can be seen from Figure 2, there were 5 different times to reach a given isoconversion point, ie, α = 0.6, for each corresponding temperature. By applying Equation 5, the activation energy can be estimated by knowing the time to reach isoconversion (t_α) and temperatures. The E_a versus α plots of the compounds tested are displayed in Figure 3. As shown in Figure 3, the average E_a can be ranked as C > D > B > A. The E_a of compound A is ~40 kJ/mol lower than the other compounds. Based solely on E_a, the results shown in Figure 3 suggest that compound A is less stable than the other compounds. Since compound C has been premilled by the raw material supply group, the E_a values obtained from this investigation may not represent the true E_a value of unmilled compound C. It is known that milling in general tends to cause stability issues for drug substances, ie, lowering of the energy barrier for drug conversion to degradant. Thus, in this case, the E_a values for unmilled compound C are likely to be higher than the E_a values from the milled samples of compound C. Results shown in Figure 3 also indicate a trend between E_a and particle size/SSA. For compounds B, C, and D, the samples with higher SSA gave lower E_a. In general, these observations agree with those reported by Guo et al[1] and Zhu and Grant[18] in which high surface/volume ratio tended to reduce the E_a of solid-state conversions. The data shown in Figure 3 also indicate that small particles have relatively uniform E_a values independent of α. In contrast, the E_a of the large particles of compounds B and D depended on α. This was particularly true for the large particles of compound D, as there was nearly 40 kJ/mol difference in E_a from α values of 0.15 to 0.85. This α dependency on E_a suggests that compounds B and D undergo multiple thermal degradation steps or mechanisms changes.[14,19] Since the E_a of the large particles of these 2 compounds move toward the values of smaller particle as the conversion proceeds, the change of surface/volume ratio discussed early can also explain these observations.

To obtain a weight loss within a reasonable time scale, TGA is commonly operated at temperatures significantly higher than pharmaceutical process/storage temperatures. Thus, the data interpretation and extrapolation from elevated to ambient temperatures must be treated with caution. Since the compounds tested here form water and impurity as degradation products, the experimental temperatures are pivotal. The upper temperature limit has to be below the melting points of the compounds to prevent interferences from the melting/evaporation of the parent compounds. One the other hand, the lower temperature limit has to be above the boiling points of the impurities to ensure that the impurities are readily evaporated and the solid-state conversion is the rate-limiting step. Preliminary data indicate that under atmospheric pressure the boiling points of all impurities are around 120ºC and the boiling point of water is 100ºC. Because of these limitations, the temperatures for this investigation were set at 135 to 165ºC. From these temperature boundaries, compound D exhibited the longest run time of ~7.5 days to
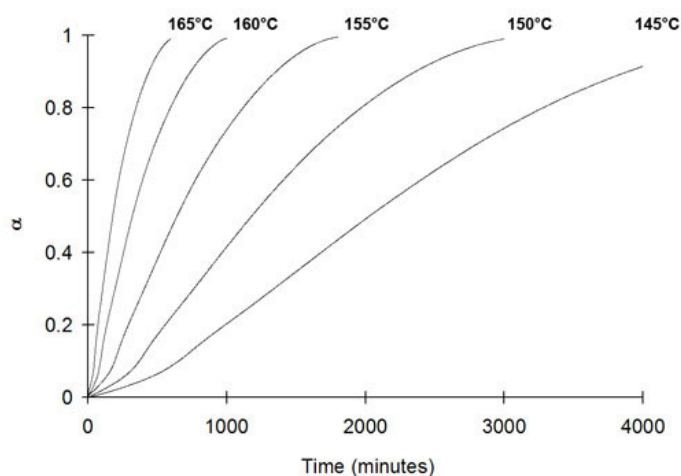
Figure 2. α-time profiles of compound D-L under different isothermal conditions.
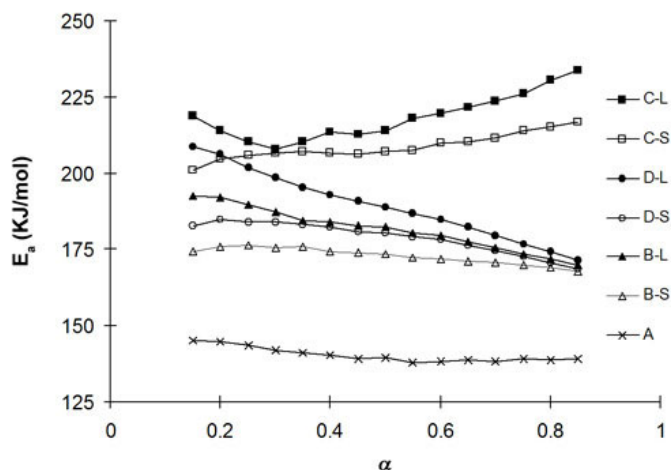
Figure 3. E_a versus α of compounds tested.

complete 1 data set. Therefore, the experimental time of estimating E_a is reduced from months to weeks compared with traditional accelerated stability studies. In addition, this approach offers several advantages on estimating the E_a for thermal degradation. For example, it requires only milligrams of sample with minimal sample preparation and sensitive down to the μg level.

The E_a values for thermal degradation of 4 exploratory compounds are measured directly without interference from excipients. For individual compounds, the E_a values correlate inversely with respect to SAA and in agreement with surface/volume hypothesis.[1,18] The E_a values between compounds cannot be compared directly owing to differences in their molecular packing and crystal morphologies, which might play a significant role on the conformation energy barrier for cyclization. Based on the thermal stability data, the exploratory teams can rank the development priority of these 4 compounds. For example, the surface area/volume ratio of compound A has to be modified via recrystallization process to improve its stability before further formulation development.

SUMMARY AND CONCLUSION

Isothermal gravimetric analysis was used to monitor the weight loss of 4 exploratory compounds as an indicator of their solid-state thermal stability. Data obtained from TGA were further processed via a model-free isoconversional method to estimate the activation energy values. These values ranged from 140 to 218 kJ/mol and were inversely related to their corresponding surface areas. Based on their activation energy values, the relative stability of these 4 exploratory compounds can be ranked as C > D > B > A and their formulation development activities can be prioritized.

ACKNOWLEDGMENTS

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