Reaction Kinetics of Solid-state Cyclization of Enalapril Maleate Investigated by Isothermal FT-IR Microscopic System

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To investigate the reaction kinetics of the solid-state degradation process of enalapril maleate, a Fourier transform infrared microspectroscope equipped with thermal analyzer (thermal FT-IR microscopic system) was used. The isothermal stability study was conducted at 120—130 °C for 1—2 h and changes in the three-dimensional plots of the IR spectra of enalapril maleate with respect to heating time were observed. The study indicates that the bands at 1649, 1728, and 1751 cm^{-1} assigned to intact enalapril maleate gradually reduced in peak intensity with heating time. However, the peak intensities at 1672 and 1738 cm^{-1} (due to enalapril diketopiperazine (DKP) formation) and at 3250 cm^{-1} (corresponding to water formation) gradually increased with heating time. The solid-state diketopiperazine formation and the degradation process of enalapril maleate *via* intramolecular cyclization were found to be simultaneous. The isothermal decomposition curves were sigmoidal and were characterized by induction and acceleration periods, indicating the presence of autocatalytic solid-state decompositions. Moreover, the power-law equation ($n=1/4$) was found to provide the best fit to the kinetics of decomposition. This isothermal FT-IR microscopic system was easily used to investigate the degradation of enalapril maleate and the concomitant formation of DKP. The solid-state reaction of enalapril maleate required an activation energy of 195±12 kJ/mol to undergo the processes of decomposition and intramolecular cyclization.

Key words solid-state decomposition; reaction kinetics; enalapril maleate; DSC; Isothermal; DKP formation; thermal FT-IR microscopic system

The stability of drugs in various solid dosage forms is an important issue, since solid dosage forms are the most common pharmaceutical formulation in clinical use. To determine the shelf life of a drug, accelerated stability testing has been performed under exaggerated conditions to examine the degradation process, to make shelf-life predictions and to calculate preliminary expiration dates.[1—3] The accelerated stability testing method is largely based on an empirical relationship of temperature to an observed chemical reaction-rate constant. Information about the room-temperature stability is then extrapolated from this accelerated data using the Arrhenius' law.[1—3] This test is generally performed under isothermal conditions, using parallel storage of samples at different temperatures.

The decomposition reactions of solids include all the chemical transformations, which involve a redistribution of the bonding forces of a crystalline reactant. The bond redistribution process usually occurs at a reaction interface to transform the reactant solid into a product.[4] The decomposition reaction-rate of a solid phase is usually assumed to be directly proportional to the area of the active interface and principally relates to the temperature dependency. Once a molecule decomposes at an activated site and changes in geometry, the neighboring molecules are more likely to degrade and cause a further decomposition reaction. In general, the decomposition reactions of solids are too complicated to show the molecular details of the solid-state reaction.[5] Some solid-state decompositions of drugs have been analyzed in terms of zero-order and first-order kinetics,[6,7] and both the Prout–Tompkins and Avrami–Erofeev equations have also been found to be the best fit for the decomposition of aspartame, cytosine monohydrate or binaphthyl.[5,8,9] Although many methods of analysis have been used to study solid-state reactions and their kinetics,[10] the combined physical analytical technique of Fourier transform infrared (FT-IR) spectroscopy equipped with a thermal analyzer is more convenient than other methods.[11—14]

The thermal-dependent characteristics of materials have been extensively studied using a thermal FT-IR microspectroscopic system, which is a simple, rapid and powerful tool for studying micro-samples.[14] It not only determines the effect of temperature on the conformation of samples, but also acts as a method for accelerated stability testing to predict product stability and shelf life. This unique system has been used in our laboratory to investigate the correlation between the structural change of samples (such as drug,[15] skin,[16] silicon elastomer,[17] Eudragits and poly(*N*-isopropylacrylamide) polymers,[18—20] α-crystallin and dipeptide sweetener[21,22] and thermal treatment. Our previous study showed that the pathway of the solid-state diketopiperazine (DKP) formation in aspartame and lisinopril via intramolecular cyclization by the nonisothermal FT-IR microspectroscopic system is almost simultaneous.[22,23] However, there are no kinetic studies or studies on the degradation of enalapril maleate and the concomitant formation of DKP. The purpose of this study was to investigate the kinetics of the degradation process and the DKP formation of enalapril maleate under isothermal conditions by time-scan measurement using the thermal FT-IR microspectroscopic system. The activation energy for solid-state decomposition reaction of enalapril maleate was also estimated.

Materials and Methods

Materials The enalapril maleate used in this study was of pharmaceutical grade. It was purchased from Chem. Works Gedeon Richter, Ltd., Hungary and was kindly donated by China Chem. & Pharm. Co. Ltd, Taipei, R.O.C. The KBr was of analytical reagent grade and was purchased from Nacalai Tesque, Kyoto, Japan.

Conventional Thermal Analysis of Enalapril Maleate The powdered sample of enalapril maleate was examined by conventional differential scanning calorimetry (DSC-910, TA Instruments Inc., U.S.A.) under non-isothermal analysis from 25 to 300 °C at heating rate of 3 °C/min and isothermal

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treatment at 125 °C, with an open pan system in a stream of N_2 gas. The DSC cell was calibrated with indium.

Isothermal FT-IR Microspectroscopic Study A powdered sample of enalapril maleate was sealed within a KBr pellet by hydraulic press (200 kg/cm^2, 15 s). This compressed KBr pellet was put directly on the DSC microscopy cell (FP 84, Mettler, Switzerland). The cell was then placed on the stage of the microscope installed in the FTIR microscopic spectrometer (Micro FTIR-200, Jasco, Japan) with an MCT detector. The system was operated in the transmission mode. The position and focus of sample were adjusted by the microscope. The IR beam was imaged onto the sample with a 16X Cassegrainian objective. The desired sample size for determination was selected and defined by means of an Aperture Through Optical System (ATOS). The temperature of the DSC microscopy cell was monitored with a central processor (FP 80HT, Mettler, Switzerland). This isothermal procedure used a time-scan measurement program to maintain the DSC microscopy cell at 120, 122.5, 125, 127.5, and 130 °C for 1—2 h, respectively. During the experiment, the sample pellet was first equilibrated to the above-prescribed temperature for about 3 min and then time-scanned. The thermal-responsive IR spectra and DSC curves were simultaneously recorded while the sample pellet was heated on the DSC microscope stage.

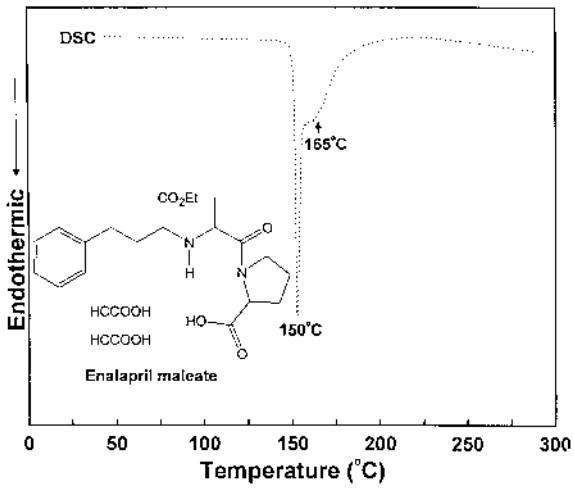

Fig. 1. The Molecular Strructure and DSC Thermogram of Enalapril Maleate

Results and Discussion

Figure 1 shows the DSC thermogram of enalapril maleate under non-isothermal treatment. Only one endothermic peak with a shoulder was obvious at 150 and 165 °C. The former was the fusion temperature of sample, but the latter might be due to the complicated reaction. It is difficult to show the DKP formation in enalapril maleate from this DSC thermogram.

The representative three-dimensional plots of FT-IR spectra of enalapril maleate between 3400—2800 and 1800—1300 cm^{-1} as a function of heating time at three different temperatures (120, 125, and 130 °C) are shown in Figs. 2A—C. These clearly show that the changes in peak intensity and frequency of IR spectra of enalapril maleate are thermal-dependent. Our previous study found that the degradation process and the DKP formation of lisinopril occur almost simultaneously by the nucleophilic attack of the *N*-secondary amine on the carbonyl group of carboxylic acids.[23] The present isothermal study revealed that the degradation-related IR peaks: at 3215 cm^{-1} (due to the secondary amine), at 1751 and 1728 cm^{-1} (corresponding to the carbonyl group of ester and carboxylic acid), respectively, at 1649 cm^{-1} (related to the carbonyl stretching of tertiary amide), at 1454 cm^{-1} (assigned to the CH_2 scissoring), and at 1379 cm^{-1} (due to the C–H bending of enalapril maleate), gradually changed in peak intensity with heating time at each isothermal temperature, but stopped at each end point of degradation. The end points of the degradation process were 88.2 min for 120 °C, 25.2 min for 125 °C and 11.6 min for 130 °C, respectively. In the meantime, three new IR bands: at 3250 cm^{-1} (assigned to the broad O–H stretching mode of water), at 1738 cm^{-1} (due to C=O stretching of ester) and at 1672 cm^{-1} (corresponding to the carbonyl band of DKP), gradually appeared with the increase of heating time and their peak intensities became progressively stronger. A detailed stereochemical analysis of DKP derivatives of enalapril has been studied by IR and NMR methods.[24] These new peaks at 1738 and 1672 cm^{-1} were also found in the IR spectra for pure DKP. Therefore, the appearance of these three new peaks during the heating process might be attributable to the solid-state degradation and the simultaneous DKP formation of enalapril maleate *via* intramolecular cyclization. It also shows that at higher temperatures the time to the end point of the reaction was shorter.

Figure 3 shows the heat and time-dependent changes in the IR peak intensity of several bands for enalapril maleate during isothermal treatment at 125 °C. The DSC curve determined by the conventional DSC with isothermal treatment at 125 °C is also displayed. Apparently, the bands belonging to the intact enalapril maleate at 1649, 1728 and 1751 cm^{-1} gradually reduced in peak intensity with heating time up to 25.2 min and therefore maintained an almost constant value. On the other hand, the peak intensity due to enalapril DKP formation at 1672, 1738, and 3250 cm^{-1} gradually increased with heating time. This strongly confirms that the degradation process and DKP formation occurred almost simultaneously in enalapril maleate. A different behavior found for peak at 3215 cm^{-1} might be due to the influence of the broad spectrum of water formation, since this peak was originally assigned to the secondary amine. This indicates that a molecular rearrangement in this complicated solid-state reaction occurred before 25.2 min. It is also noted that the peak intensity of the sample should be kept constant after 25.2 min to show the complete reaction, but a slight increase was found. Both the degradation process and the DKP formation detected from the thermal FT-IR microscopic system occurred at almost the same time, but the conventional DSC curve did not show any obvious thermal change. The reason is unclear, but was perhaps due to the compensating effect during the simultaneous reaction.

To investigate the process of degradation and DKP formation of enalapril maleate in more detail, the first derivative was calculated for each line in Fig. 3 and is shown in Fig. 4. The positive ΔAbs value represents the DKP formation but the negative ΔAbs value reveals the process of degradation. It is also evident that the reaction rate for DKP formation and for the degradation process was enhanced with the increase of heating time, suggesting that an autocatalytic reaction in enalapril maleate drove both reactions. These ΔAbs values were maximized at 22.2 min. Beyond 22.2 min, the reactant of enalapril maleate was consumed and the ΔAbs value was near zero. The time of maximum reaction rate for the degradation process and DKP formation was similar, implying the thermal-related reaction in the molecules of enalapril maleate

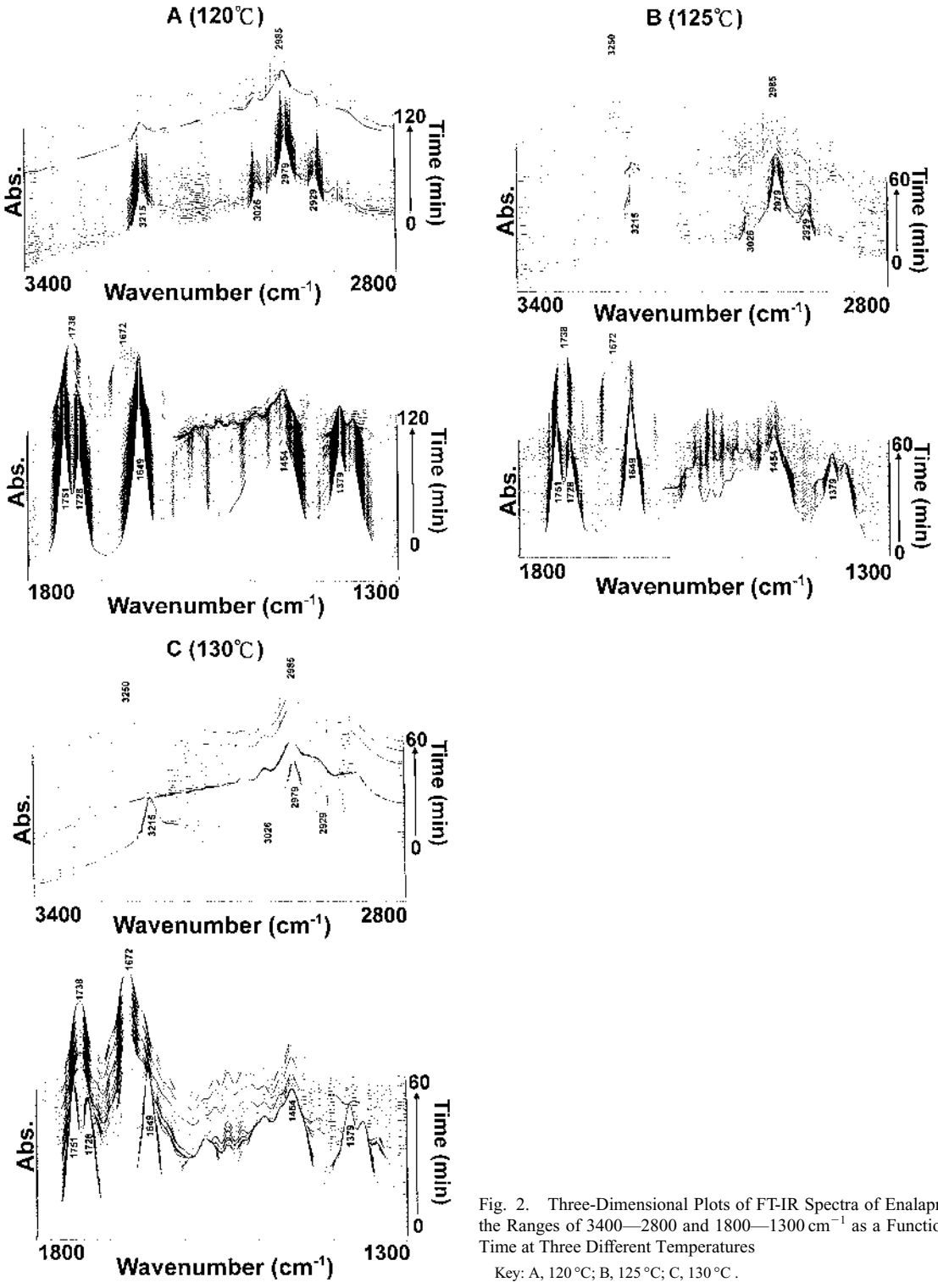

Fig. 2. Three-Dimensional Plots of FT-IR Spectra of Enalapril Maleate in the Ranges of 3400—2800 and 1800—1300 cm^{-1} as a Function of Heating Time at Three Different Temperatures

Key: A, 120 °C; B, 125 °C; C, 130 °C .

was transformed simply and simultaneously from reactant to product. Although the formation of water and DKP also occurred simultaneously in the reaction, a lower intensity of 3250 cm^{-1} was observed in Figs. 3 and 4. The loss of water from the KBr pellet compressed during the heating process might have been responsible for this result.

Figures 3 and 4 also reveal that the degraded change in intensity was more pronounced for the peak at 1649 cm^{-1} than other peaks. Thus this peak was used as a reference to determine the kinetics of the degradation process of enalapril maleate during heating. Since the end point of the reaction was 25.2 min, the reaction of degradation and DKP formation should have been complete. The fraction decomposed, α, can be expressed by

$$\alpha = 1 - \left(\frac{A_{(t,T)} - A_{(25.2,T)}}{A_{(0,T)} - A_{(25.2,T)}} \right)$$

where, $A_{(t,T)}$ is the peak intensity at 1649 cm^{-1} at temperature T for time t, and $A_{(25.2,T)}$ is the peak intensity at 1649 cm^{-1} at

temperature T for 25.2 min. The plot of the fraction decomposed as a function of time at different temperatures is shown in Fig. 5. Obviously, the induction and acceleration periods characterize the isothermal decomposition curves. The shape of the curves is sigmoidal, indicating an autocatalytic solid-state decomposition.[25] It is apparent that the rank order of the degradation process is 130 °C>127.5 °C>125 °C>122.5 °C>120 °C. The higher the temperature, the shorter the reaction time obtained. In addition, except at 130 °C, an induction period was clearly observed. The lower the temperature used the longer the duration of the induction period seen. This implies that the degradation process in enalapril maleate was temperature-dependent.

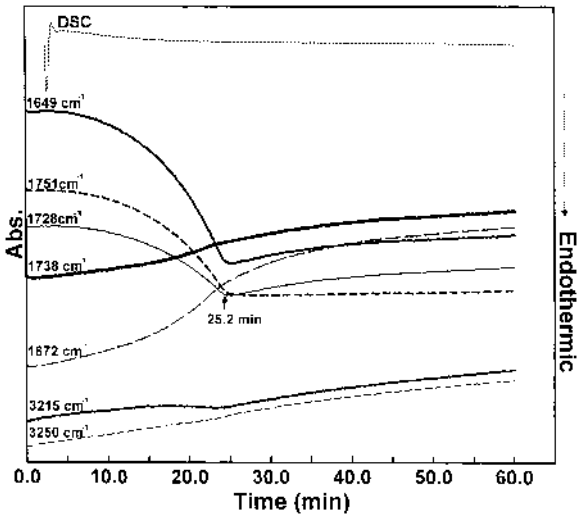

Fig. 3. The Conventional DSC Curve and Time-Dependent Changes in the Peak Intensity of Several IR Bands for Enalapril Maleate during Isothermal Treatment at 125 °C

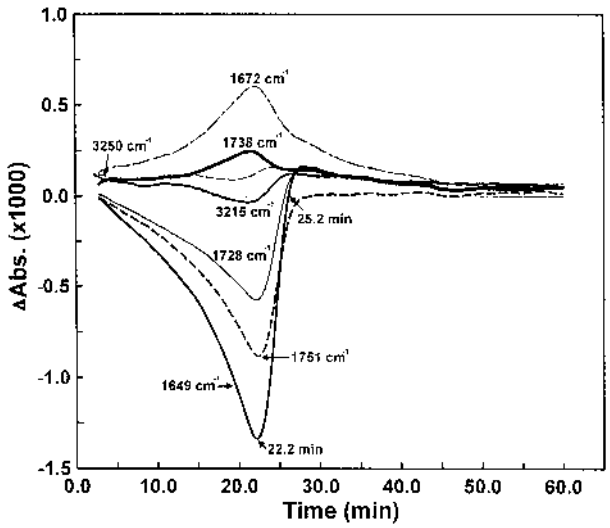

Fig. 4. First Derivatives of the Curves from Fig. 3

The values of α and the time obtained from Fig. 5 were entered into a personal computer previously programmed with several kinetic equations of solid-state reactions,[5,26] and then fitted to a model. The best fitted slopes and determining coefficient (r^2) from the least-squares analysis of the data were obtained and are listed in Table 1. The result showed that the reaction curves of enalapril maleate in the isothermal process could be model-fitted by different kinetic equations, which assume various mechanisms. According to the values of determining coefficient (r^2) of each equation for every isothermal temperature, however, the power-law equation seemed to provide a good fit ($r^2>0.98$) to the kinetic profile in which the power-law equation ($n=1/4$) was the best-fitted ($r^2>0.999$). This was consistent with the power-law for the acceleratory rate equation that is usually a feature of the isothermal kinetics of solids.[27] The power-law equation suggests that the decomposition mechanism of enalapril maleate under the isothermal process was multi-step nucleation,

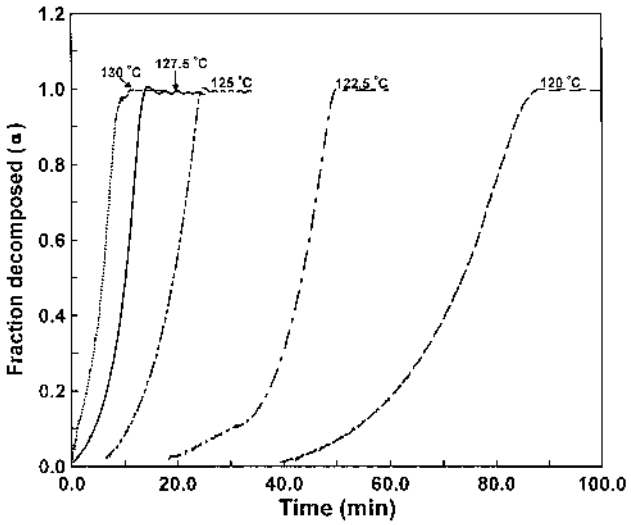

Fig. 5. The Plot of the Fraction of Decomposed Enalapril Maleate as a Function of Time at Different Temperatures

The curves are labeled with the temperatures used.

Table 1. Results of Application of Five Solid-State Kinetic Equations to Data from the Thermal Decomposition of Enalapril Maleate

Temperature (°C)	Rate constant k (s^{-1})×1000				
	Power-law $\alpha^n=kt$ ($n=1/4$)[a]	Power-law $\alpha^n=kt$ ($n=1/3$)	Power-law $\alpha^n=kt$ ($n=1/2$)	First order $\ln(\alpha)=kt$	Avrami–Erofeev ($n=1/4$)
120.0	13.8 (0.999)*	16.6 (0.999)*	20.7 (0.993)*	75.0 (0.991)*	20.2 (0.969)*
122.5	20.3 (0.999)*	24.3 (0.997)*	29.7 (0.987)*	114.1 (0.995)*	28.5 (0.963)*
125.0	31.2 (0.999)*	37.8 (0.999)*	47.0 (0.994)*	169.5 (0.972)*	45.8 (0.964)*
127.5	46.7 (0.999)*	56.6 (0.996)*	70.5 (0.987)*	253.3 (0.997)*	54.0 (0.964)*
130.0	57.9 (0.996)*	70.5 (0.997)*	88.9 (0.995)*	307.6 (0.981)*	89.0 (0.969)*

* The determinating coefficient (r^2) of the best-fitted kinetic equation ($0.05<\alpha<0.95$). *a*) The induction period calculated by power-law ($n=1/4$) in 120, 122.5, 125, 127.5, and 130 °C is 41.5, 20, 7.8, 2.4, and 0 min, respectively.

which pointed out that the formation of a stable growth nucleus required the successive molecular decompositions at a single site.[27,28] The induction period is also listed in Table 1; the higher the temperature used the shorter the induction period required.

The activation energy (*Ea*) of the decomposition for enalapril maleate can be determined by an Arrhenius equation as follows:

$$k = A \exp(-Ea/RT)$$

where k is the reaction rate constant, A is a frequency factor, R is the gas constant and T is the absolute temperature. A plot of $\ln k$ obtained from the above power-law equation ($n = 1/4$) against $1/T$ was obtained. A good linear relationship was obtained with higher correlation coefficient ($r > 0.995$), and its activation energy was calculated from the slope (Ea/R). The activation energy was 195.2 (11.2 kJ/mol, suggesting that the solid-state reaction process of enalapril maleate needed this activation energy to undergo the decomposition and intramolecular cyclization.

In conclusion, the thermal FT-IR microscopic system was easily used to investigate the degradation process of enalapril maleate and the concomitant formation of DKP. The processes of decomposition and intramolecular cyclization in the solid-state enalapril maleate required about 195 ± 12 kJ/mol of activation energy.

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