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The thermal analysis study of the drug captopril

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Abstract

Captopril is an antihypertensive drug currently being administered in tablet form. The thermal analysis study was carried out using a simultaneous TG–DTA unit. Both the isothermal and non-isothermal experiments are preformed to investigate the thermal degradation process of captopril in its natural state as a solid. The runs were performed in a flowing nitrogen atmosphere. Captopril melted at 106°C followed by decomposition. Based on the order of reaction, one method is used to identify the reaction mechanism in isothermal kinetics and two methods are used to identify the reaction mechanism in non-isothermal kinetics. These methods use the equations established by Avrami–Erofeev, Arrhenius and Freeman and Carroll. However, a kinetic analysis based on the ''method of fit'' using zero-order, first-order, and second-order equations showed that a first-order process gave a good fit for the Arrhenius plot at certain specific experimental conditions (i.e. very low sample mass). Overall, a second-order process followed by a first-order reaction for the main decomposition process of captopril showed an even better fit for the experiments. The possible reasons for this kinetic behavior are presented. There was up to 2% carbon remaining at 500°C. Thermal analysis was supplemented using Fourier Transform infrared spectroscopy (FTIR), X-ray diffraction and scanning electron microscopy (SEM) methods to identify the captopril with any degradation products which may have formed.

Keywords: Captopril; Arrhenius method; Freeman and Carroll method

1. Introduction

The interactive nature of captopril used in tablet formulations is the subject of the present investigation. Ford and Timmins [1] pointed out the use of thermal analysis in the characterization of pharmaceutical solids and the use of thermal analysis in the development of solid dosage forms. In order to determine the potential problems of mixing excipients with captopril, the decomposition process of captopril alone must be stated initially. In the present study, the decomposition rate of captopril was studied using isothermal and rising temperature methods on a simultaneous thermal analysis TG–DTA unit. Once the reaction kinetics for captopril is established, it can then be applied to investigate the stability and interaction of captopril with excipients used in the tablet formulation.

One main purpose for the kinetic analysis of solid decomposition is to determine the reaction mechanism(s) and to calculate the Arrhenius parameters. 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 [2]. In a review paper, Dollimore and Lerdkanchannaporn

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[3] reviewed recent published papers in the thermal analysis field. They commented on the steps needed to determine the reaction kinetics from thermal analysis data. Dollimore also pointed out the priority of the steps outlined is often lost in the analysis from rising temperature data.

The mechanism of an isothermal reaction in solid state can be defined using the Hancock and Sharp equation [4]. Based on this standard equation for the analysis of nucleation and growth processes, the kinetics for isothermal solid-state reactions can be represented by the following equation:

$$\ln[-\ln(1-\alpha)] = \ln k + n \ln t \tag{1}$$

where α is the fraction reacted in time t, k a constant which depends in part on the nucleation frequency and linear rate of grain growth and n a constant that can vary according to the reaction (see Table 1).

In an infinitesimal time interval, the non-isothermal reaction process can be considered as an isothermal one and the rate of a solid-state decomposition reaction may be expressed as

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = k(T) f(\alpha) \tag{2}$$

where α is the fraction decomposed, $f(\alpha)$ a function of the actual composition of the sample and $k(T)$ the temperature dependent specific rate constant which is given by the Arrhenius equation, given below:

$$k(T) = A \exp\left(-\frac{E}{RT}\right) \tag{3}$$

Table 1
Values of n for a solid-state reaction rate equation [5]

Mechanism symbol	Slope n
El	1.06
A2	2.00
A3	3.00
A4	4.00
R2	1.11
R3	1.08
Dl	0.62
D2	0.57
D3	0.54
D4	0.58
Fl	1.00
F2	1.48
F3	0.74

where E is the activation energy, A the pre-exponential factor, R the gas constant and T the absolute temperature.

Combining Eqs. (2) and (3) then gives

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = A \exp\left(-\frac{E}{RT}\right) f(\alpha) \tag{4}$$

where α is the fraction reacted in time t and the function $f(\alpha)$ depends on the reaction mechanism and the geometry of the reacting mechanism and the geometry of the reacting particles [2].

The $f(\alpha)$ in Eq. (3) may be assumed as

$$f(\alpha) = (1-\alpha)^n \tag{5}$$

The main equation used in this study can be arranged as follows:

$$k_n = \frac{[(\mathrm{d}\alpha/\mathrm{d}T)\beta]}{(1-\alpha)^n} \tag{6}$$

where k_n is the rate constant of the nth order, α the fraction decomposed, n the order of reaction (zero-, first- or second-order reaction) and β the heating rate.

In order to determine the decomposition process for captopril, a kinetic analysis based on the ''method of fit'' using zero-order, first-order and second-order equations were used to determine the best fit for the Arrhenius plot. This can be done by applying the calculated k_n in the Arrhenius equation. Therefore, to substitute k_n into Eq. (3) gives

$$k_n(T) = A \exp\left(-\frac{E}{RT}\right) \tag{7}$$

and the natural logarithm of this equation would be

$$\ln k_n(T) = \ln A + \left(-\frac{E}{R}\right)\left(\frac{1}{T}\right) \tag{8}$$

Thus, plotting the $\ln k_n(T)$ against $(1/T)$ can give a regression line as $y = ax + b$. Where the activation energy E can be calculated from the slope a times the gas constant R.

The Freeman and Carroll method [6] is also used in the kinetic analysis of solid-state decomposition processes. This method is known as the difference-differential method. The first determining mass-loss conversion and rate; reciprocal of temperature at some points on the TG curve; then their differences between two adjacent points can be determined from one

thermal analysis curve. Kinetic parameters can then be obtained schematically according to the following equation:

$$-\left(\frac{E}{2.303R}\right)\left[\frac{\Delta(1/T)}{\Delta\log W_r}\right] = \left[\frac{\Delta\log(dw/dt)}{\Delta\log W_r}\right] - n \qquad (9)$$

where W_r is the difference between the weight loss at the completion of the reaction and the weight loss W up to time t, dw/dt the mass-loss rate at time t, T the temperature in K, n the order of reaction, E the activation energy in kJ mol^{-1} and R the gas constant in 8.314 J mol^{-1} K^{-1}.

From the plot of $[\Delta\log(dw/dt)/\Delta\log W_r]$ against $[\Delta(1/T)/\Delta\log W_r]$, the slope of the straight line can be used to calculated the activation energy. Then $E\,(\text{kJ mol}^{-1}) = \text{slope} \times 2.303 \times 8.314$ and n (order of reaction) can be obtained from the intercept of the straight line. When the mass-loss rate obviously changes, the selected temperature interval should be decreased.

2. Materials and methods

Materials. The active ingredient captopril ($C_9H_{15}NO_3S$; [2S]-1-[3-mercapto-2-methyl propionyl]-L-proline) was obtained from Sigma (lot No. 37H1120).

Instruments. The thermal analysis equipment consisted of a simultaneous TG–DTA unit, TA Instruments Model No. 2960. The experimental data was analyzed with TA Instruments Universal Analysis Software, V2.3C.

The FTIR pattern for captopril was performed on the Nicolet 5DX FTIR. The software package [7] controls data acquisition, acquisition parameters, post acquisition processing and graphic presentation of data obtained from the Nicolet 5DX FTIR IR bench. It is designed around an IBM PC compatible computer equipped with a math coprocessor (optional), EGA graphics card and mouse.

A powder diffraction pattern was obtained using the Scintag XDS 2000, mounted on an X-ray generator, operating at the Cu Kα wavelength, 45 kV and 40 mA. The experimental pattern for captopril was compared with patterns obtained from the JCPDS database. The XRD and SEM pattern for captopril were analyzed by the Instrumentation Center at the University of Toledo.

Procedures. The TG–DTA experiments were carried out in a dry nitrogen atmosphere at a flow rate of 100 ml min^{-1} in a platinum crucible with an empty platinum crucible as a reference. In this heat treatment, captopril was employed without any further treatment. In the isothermal experiments, the isothermal temperature was jumped from 180 to 260°C using 10° interval. For every isothermal run, the experiment was run for 1 h. For the non-isothermal experiments, the sample mass was varied from 2.7 to 16 mg. The heating rate β was varied from 2 to 12°C min^{-1} and heated to 700°C.

3. Results

3.1. Isothermal runs

3.1.1. Thermal curves

The overlay plots resulting from the time (min) versus weight (%) plots at different isothermal temperatures are seen in Fig. 1. Such plots show that a large decrease in weight occurred in the first 5 min and then a continuous weight loss can be seen. It should be noted that the isothermal temperature is not established at once so for the reason noted above, therefore the first 10 min of data were not used in the kinetic analysis. An example of a temperature-time plot superimposed on a mass-loss plot is seen in Fig. 2 and is explained above. It can be seen that the rate of weight loss is dependent on the isothermal temperature from those overlay curves. The higher the isothermal temperature used the faster the rate of weight loss.

The sample masses used in the isothermal experiments were 9.69–10.48 mg. The problem in using isothermal data collected over a period of 60 min is that the final weight loss is difficult to assess. One method would be to plot the logarithm of percent final weight ($1\log \%W_f$) against the reciprocal isothermal temperature (K^{-1}). From this linear regression method, the equation for the line is $y = 1797.8x - 2.1206$, where $x = 1/T$ (T in K), $y = 1\log \%W_f$ and a $R^2 = 0.9806$ are obtained. When the temperature equals infinity, $1/T$ is almost equal to 0. Hence, the intercept is equal to $-2.1206 = \log \%W_f$ and the final

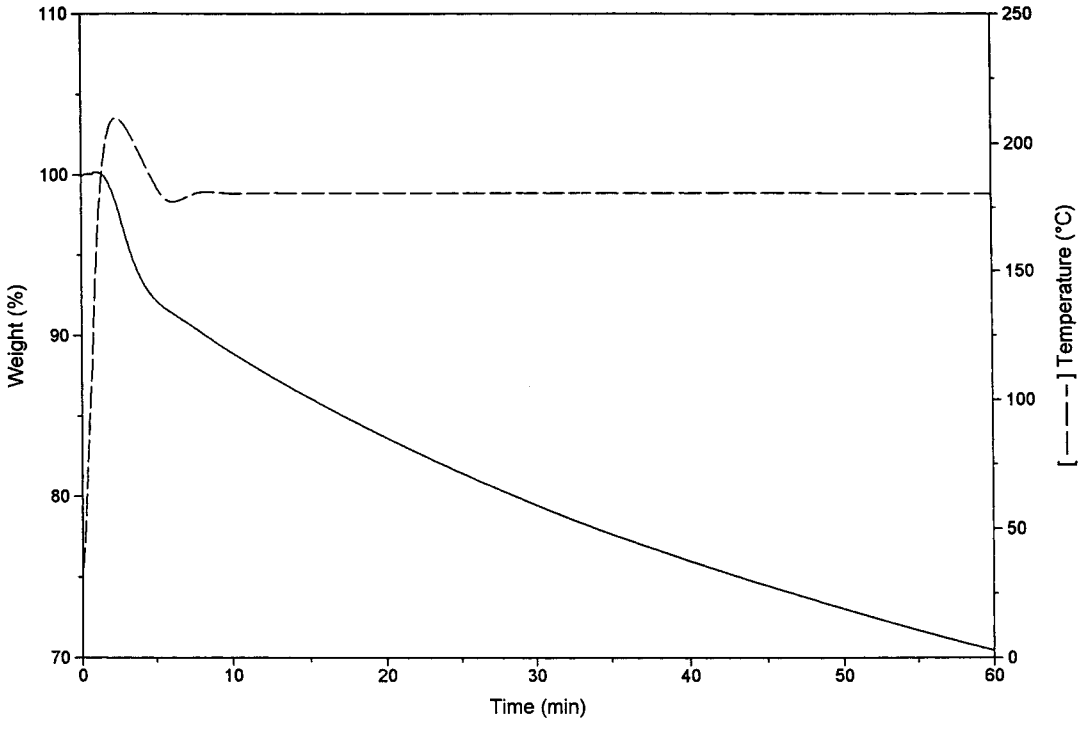

Fig. 1. The overlay plots resulting from time versus percent weight for captopril at different isothermal temperatures, under dry nitrogen at a flow rate of 100 ml min^{-1}.

$\%W$ at infinite temperature can be calculated as 0.00758%. Therefore, this $\%W$ value obtained can be taken as the final $\%W$ for isothermal kinetic analysis. In view of this value it would seem practical to take $\%W_f$ as zero, so the α value can be calculated.

The initial $\%W$ is taken at a time when the isothermal temperature first reached a steady state. Therefore, the α value can be calculated from these identified points as

$$\alpha = \frac{\%W_i - \%W_t}{\%W_i - \%W_f} \tag{10}$$

Using these α values in Eq. (1), the plot of $\ln[-\ln(1-\alpha)]$ against $\ln t$ gives the relationship curves. The α-range, slope, intercept and R^2 values obtained from these curves are listed in Table 2 for each isothermal experiment. It is known that the isothermal mechanism can be obtained from the slope n and the reaction constant k can be obtained from the intercept $\ln k$. Table 2 shows that the n value is 1.46 for the lower isothermal temperature, i.e. 180°C, and is 1.03 for the higher isothermal temperature, i.e. 260°C. These two experimental n values shown in Table 2 are close to the theoretical n values from Table 1 which lists the n values for the first-order reaction as 1 and for the second-order reaction as 1.48. The isothermal mechanism for captopril, therefore can be taken as a second-order reaction when the isothermal temperature is at 180°C and as the first-order reaction when the isothermal temperature is at 260°C.

3.1.2. Based on the order of reaction

There is another method which can be used to investigate the isothermal reaction for captopril. This can be determined by the deceleratory α versus t curves based on the order of reactions.

If the process is second order, then the equation is

$$\frac{1}{1-\alpha} = kt \tag{11}$$

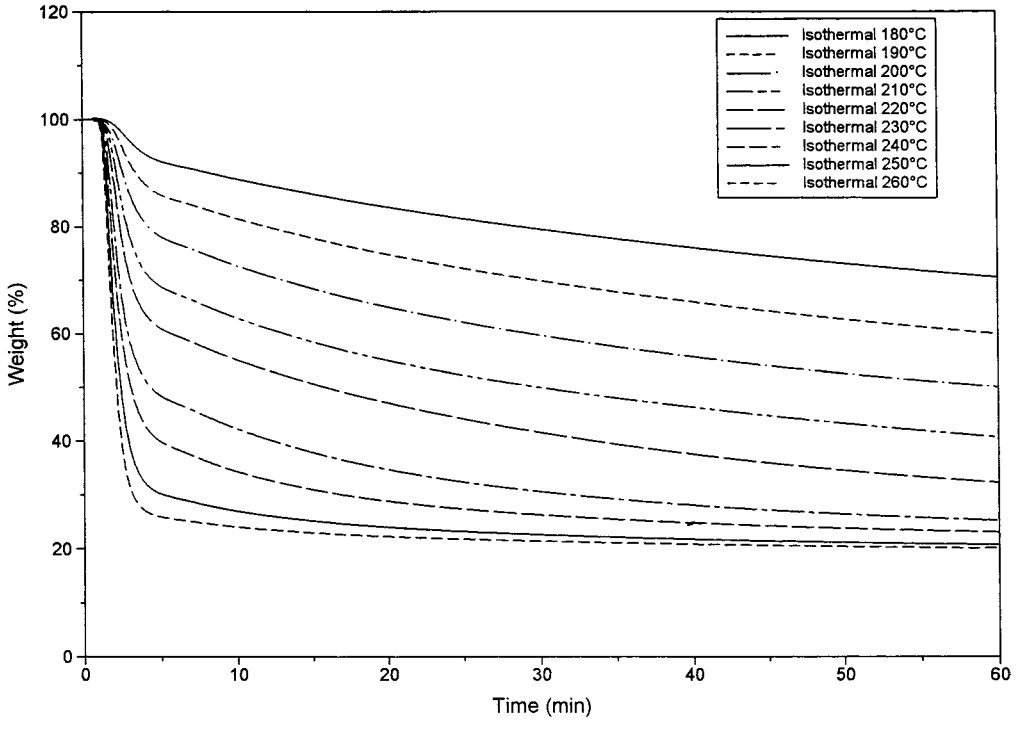

Fig. 2. The percent weight (%*W*) versus time (min) plot and temperature versus time (min) plot from isothermal runs for captopril under an atmosphere of dry nitrogen.

plots of t against $1/(1-\alpha)$ should have a slope of k. The values of $k_{2(\text{second order})}$ for each isothermal run can be assigned the follow values of k_2. A plot of $\ln k_2$ against reciprocal temperature K^{-1} then gives the plot. The slope is $-E/R$ when E can be calculated as $-\text{slope} \times R$. Thus, the slope has an R^2 value of 0.8636 and has an equation given as

$$y = -7998.7x + 12.272 \quad (12)$$

The activation energy from the data range 180–220°C can be calculated from Eq. (12) as

$$E = 7998.7 \times \frac{8.314}{1000} = 66.5 \ \ (\text{kJ mol}^{-1}) \quad (13)$$

Similarly, the first order expression can be given by the equation:

$$k_1 t = -\ln(1-\alpha) \quad (14)$$

Table 2
The isothermal mechanism results for captopril using the log–log kinetic analysis method obtained from the data range 17–55 min at different isothermal temperatures assuming W_i at T_i and W_f equal to 0

Isothermal temperature (°C)	α range	nth order (slope)	R^2
180	0.030–0.583	1.46	0.9785
190	0.042–0.245	1.41	0.9771
200	0.055–0.278	1.35	0.9735
210	0.066–0.313	1.31	0.9752
220	0.076–0.374	1.38	0.9721
230	0.095–0.361	1.13	0.9547
240	0.084–0.286	1.00	0.9513
250	0.057–0.199	0.99	0.9525
260	0.037–0.140	1.04	0.9627

A plot of t against $-\ln(1-\alpha)$ allows the slope of k_1 to be calculated. The value for the slope from this plot can be represented as k_1. The plot of $\ln k_1$ against $1/T$ can obtain a slope. The E value can be calculated from the slope as $E = -\text{slope} \times R$. Thus, the slope has an R^2 value of 0.9894 and represents the equation

$$y = -4410.4x + 4.3576 \quad (15)$$

The activation energy from the data range 180–220°C can then be calculated from Eq. (15) as follows:

$$E = 4410.4 \times \frac{8.314}{1000} = 36.66 \ (\text{kJ mol}^{-1}) \quad (16)$$

3.2. Non-isothermal runs

3.2.1. Thermal curves

The shape of all the TG/DTG curves and DTA curves for captopril were similar or nearly identical as seen in Fig. 3(a) and (b). The TG, DTG data shows a DTG curve which is roughly symmetrical about a peak temperature. Captopril by itself decomposes over the temperature range 160–450°C. A small residue of carbon was left at the end of the experiment. All the experimental plots on the TG curve show two decomposition steps using a dry nitrogen atmosphere at a flow rate of 100 ml min^{-1}. Depending on the experimental condition, the onset weight loss temperature was around 160°C and followed the second step at 290–310°C from the TG curve readings. The first noticeable small blip on the DTG curve is the peak temperature for the melting of captopril. Only a sample weight of 2.715 mg gives a sharp peak on the DTG curve (Fig. 4) at the first step of decomposition. Other sample weights ranged from 3.5 to 16 mg and gave two overlapping peaks in the first step of decomposition. The maximum signal (temperature) from the DTA curve provides a very sharp peak and represents the melting point of the material tested. A shallow broad curve can also be discerned. The melting point of the material causes the first sharp peak and the decomposition of the captopril occurs in the region of the second shallow peak.

The overlay plots (Figs. 4 and 5) show the weight dependence on the rate of decomposition. These overlay plots indicate that the rate of decomposition of captopril increases when the amount of the sample increases. Data obtained for various masses of captopril show these temperatures shifted to higher temperatures when the amount of sample increased. The same data also shows that the weight loss range for the small amount of sample is bigger than that for the larger amount of sample. The explanation for this variability may be that when the amount of sample is small, the temperature gradient from outside to inside the sample decreases. The atmosphere gas makes the temperature surrounding the sample uniform and reduces the temperature difference between the sample and sample holder. This also can be seen in the superimposed plot (see Fig. 6) from various heating rates for captopril. This figure shows that the curve temperatures shifted to the higher temperature and the remaining amount of sample increased when the heating rate increases. This result suggests the manner in which the heating rate influences the temperature distribution inside the sample. This also suggests that the various heating rates effect the distribution of heat flux from the atmosphere, to the crucible and then into the samples.

3.2.2. Kinetic analysis

The decomposition mechanisms for captopril in solution have been established by Lee [8]. In his research, captopril was decomposed by all possible mechanisms including zero-order, first-order and second-order reactions depending on the experimental conditions. In this study, two methods were used in the rising temperature kinetic analysis for captopril. For most reactions involved in thermal methods, the rate laws are complex, but it is important to realize that the rate of change will depend very greatly on two factors: (a) the amount of substance reacting and (b) the temperature. Thus, these kinetic analysis methods are not only focused on the order of a reaction mechanism but also can be used to calculate the activation energy for those samples under different conditions.

3.2.3. Arrhenius method

In order to determine the decomposition process for captopril, a kinetic analysis based on the ''method of fit'' using zero-order, first-order and second-order equations were used to determine the best fit for the Arrhenius plot. This can be done by applying the calculated k_n in the Arrhenius equation.

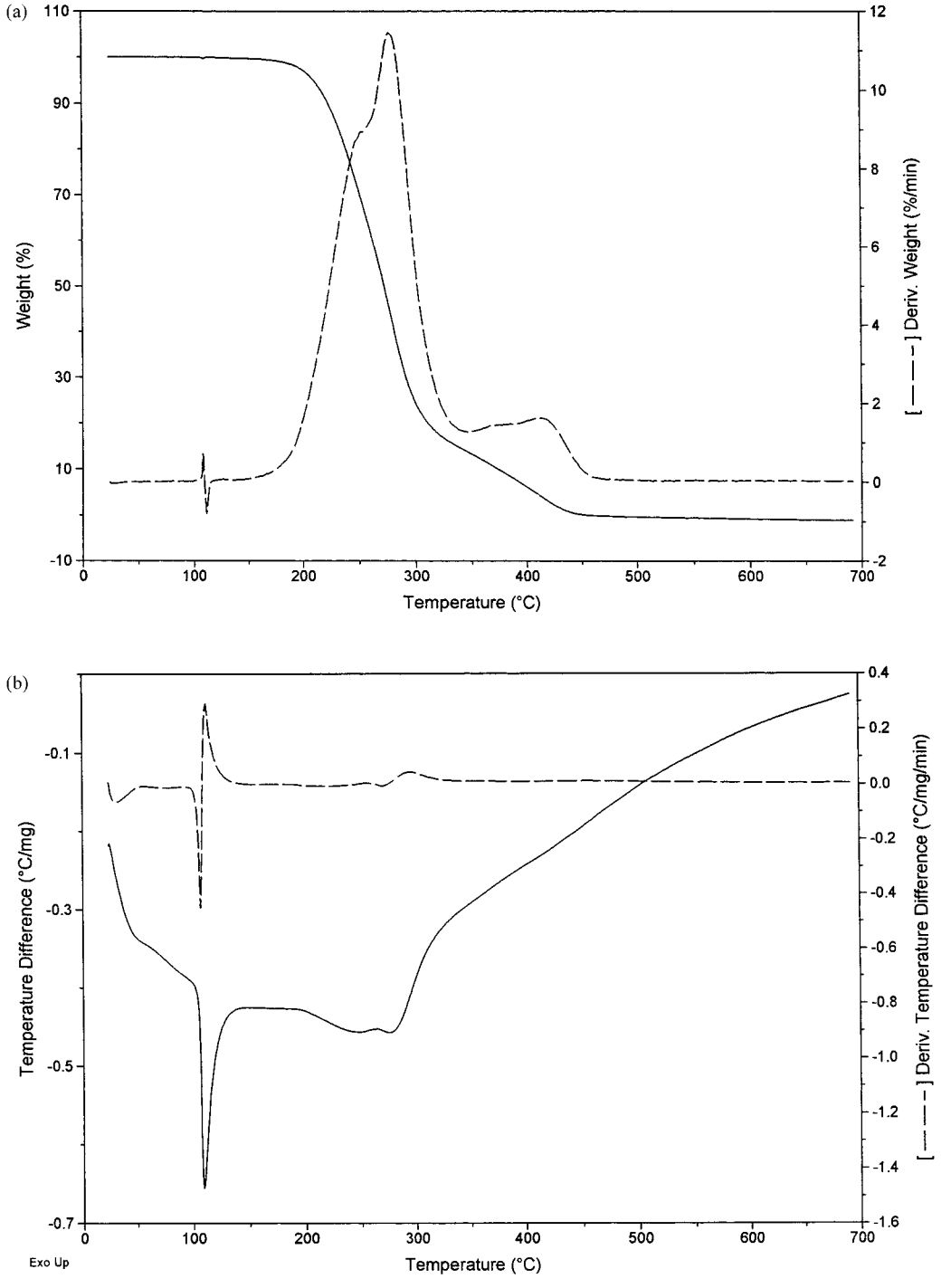

Fig. 3. A typical experimental: (a) TG/DTG plot and (b) DTA plot for captopril using dry nitrogen at a flow rate of 100 ml min^{-1}.

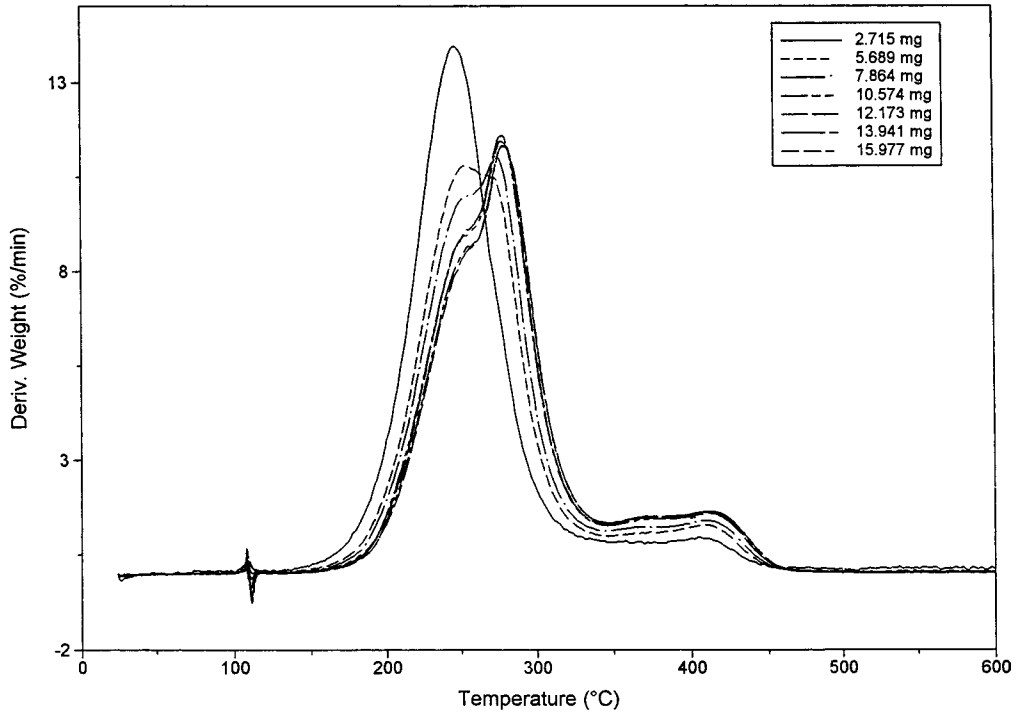

Fig. 4. Overlaid DTG curve for captopril using different sample sizes at a heating rate of 10°C min^{-1} under an atmosphere of dry nitrogen.

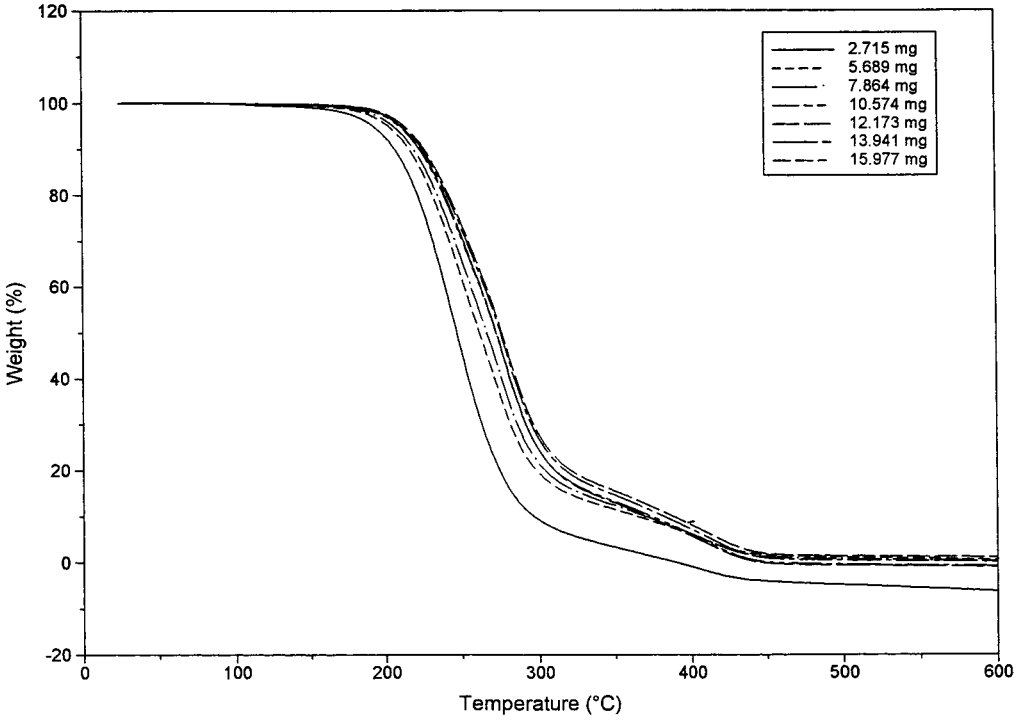

Fig. 5. Overlaid TG curve for captopril using different sample sizes at a heating rate of 10°C min^{-1} under an atmosphere of dry nitrogen.

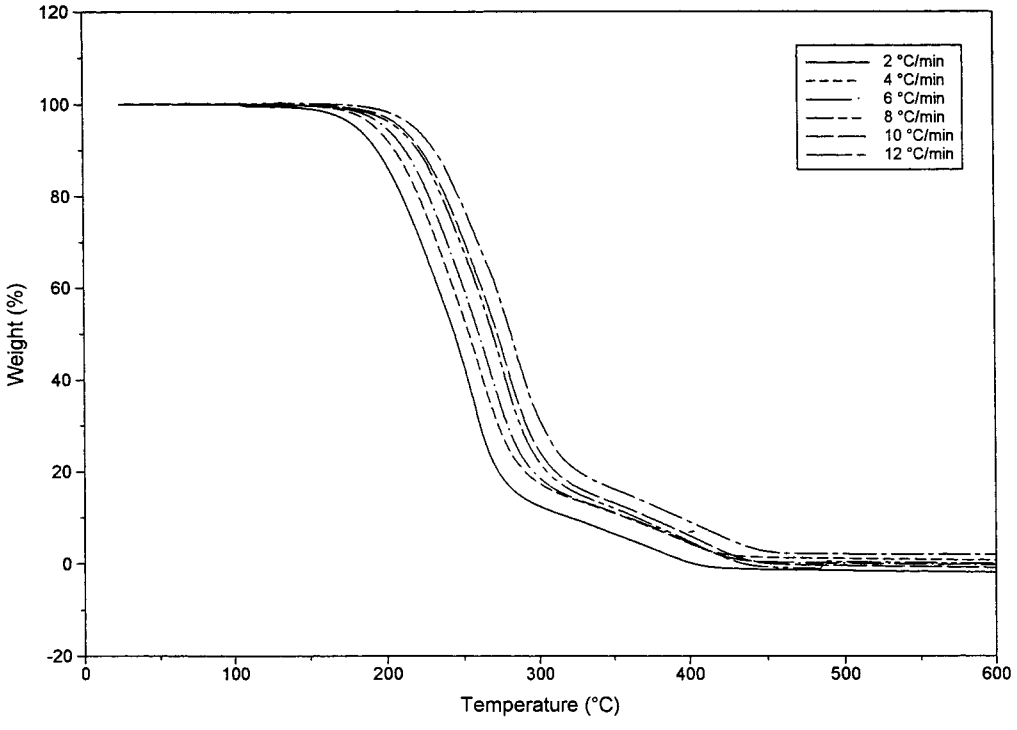

Fig. 6. Overlaid TG curve for captopril using different heating rates under an atmosphere of dry nitrogen.

The problem associated with this kinetic analysis is that there are no distinct peaks or slopes that can be obtained from the TG or DTG curves for captopril in this study. This makes it difficult to distinguish between the decomposition reactions where certain steps begin and stop which would effect the α values in the kinetic calculations. The α values at temperature T will be affected by the data values used as the initial weight W_i and final weight W_f. Therefore, two plots from the data range T_i–T_{p1} and T_{p1}–T_{p2} are produced for further kinetic analysis instead of just one plot from the whole data range T_i–T_{p2} using two overlapped peaks to represent the decomposition reactions. The data ranges for these two plots are from the decomposition peak temperatures based upon the data obtained from the DTG curves. These types of plots show better linear relationships than those taken from the data range from the TG curves without being concerned with two overlapped reactions. An example of plots of this type is seen in Figs. 7 and 8. The results from these types of plots are organized in terms of the data range plotted, initial and final weight range used, and the order of reaction assumed. The activation energy E_{act}, Ln A and R^2 values are also reported in the tables.

3.2.3.1. Effect of various sample weights. The activation energy E_{act}, Ln A and R^2 values from the "method of fit" for the various ordered reactions based on the Arrhenius equations for various sample weights are calculated. The results show that the first-order reaction for captopril is more dominant at a sample weight of 2.7 mg, but is totally masked by the second-order reaction as the sample weight increases to 5.7 mg. The second-order reaction is more dominate again when the sample weight increases above 10.5 mg. It can be concluded that there is a second-order reaction over the first data range T_i–T_{p1} from the slope of the overlapping peak. The conclusion must be made that the order for decomposition is a first-order reaction for the second data range T_{p1}–T_{p2} for captopril using an appropriate sample size. This can be seen in Table 3. The activation energy for the first step decomposition reaction assuming a second-order reaction is between 107.4 and 109.0 kJ mol^{-1}. The activation

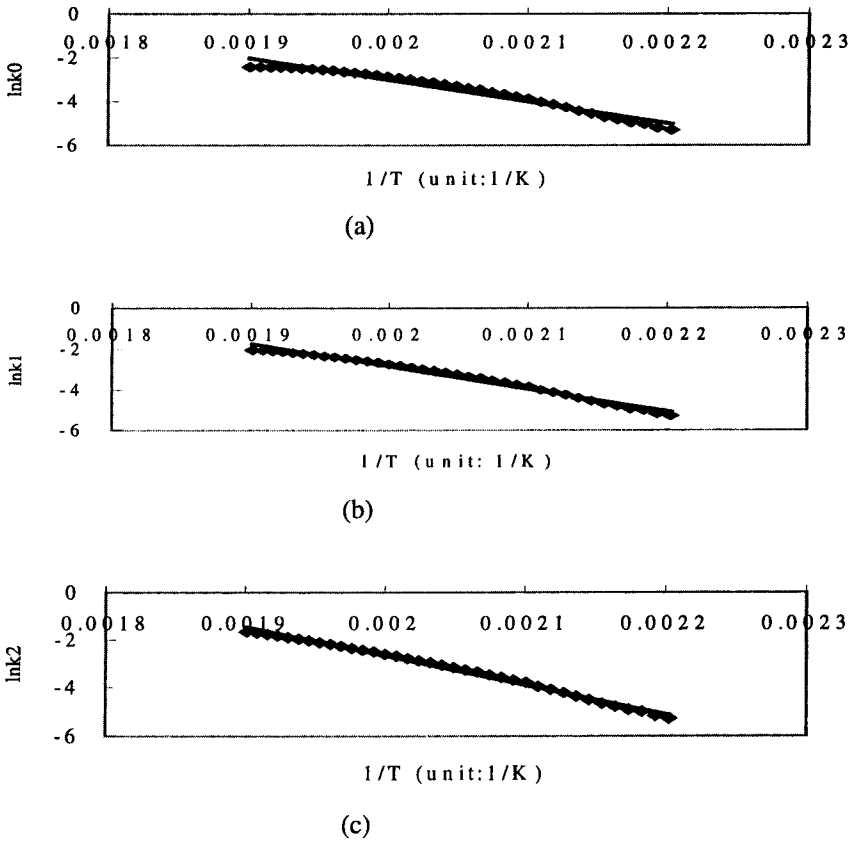

Fig. 7. Plot of the ln k against the reciprocal of temperature $1/T$ for captopril from the data obtained under the experimental conditions of 10°C min dry nitrogen 100 ml min^{-1}, sample weight of 10.56 mg using the Arrhenius equation assuming the (a) zero order where $R^2 = 0.9612$, slope $= -9974.6$ and an intercept of 16.939; (b) first order where $R^2 = 0.9813$, slope $= -11106$ and an intercept of 19.37; (c) second-order reactions where $R^2 = 0.9924$, slope $= -12237$ and an intercept of 21.8. (Plot for the data range from 181 to 253°C under the assumption of $\%W_i = 100$ and $\%W_f = 0\%$.)

energy for the second-step decomposition reaction assuming a first-order reaction is between 94.3 and 123.9 kJ mol^{-1}.

3.2.3.2. Effect of various heating rates. The activation energy E_{act}, Ln A and R^2 values were calculated from the "method of fit" for the various ordered reactions based on the Arrhenius equations. A comparison of the linear regression values from various heating rates, shows that good R^2 values can be obtained from first- and second-order assumptions. The overall R^2 values are at least equal to 0.99 at the heating rate ranges 6–10°C min^{-1}. The results from various heating rates are based on the assumption of a second-order reaction followed by a first-order reaction as the various sample weights are altered. The results under this assumption are compared and listed in Table 4. This table shows that the various heating rates effect the activation energy obtained for captopril and suggests that the optional experimental heating rates used for captopril should be between 6 and 10°C min^{-1}. The activation energy for the first step decomposition reaction assuming a second-order reaction has values between 91.4 and 107.6 kJ mol^{-1}. The activation energy for the second step decomposition reaction assuming a first-order reaction is between 109.0 and 178.4 kJ mol^{-1}.

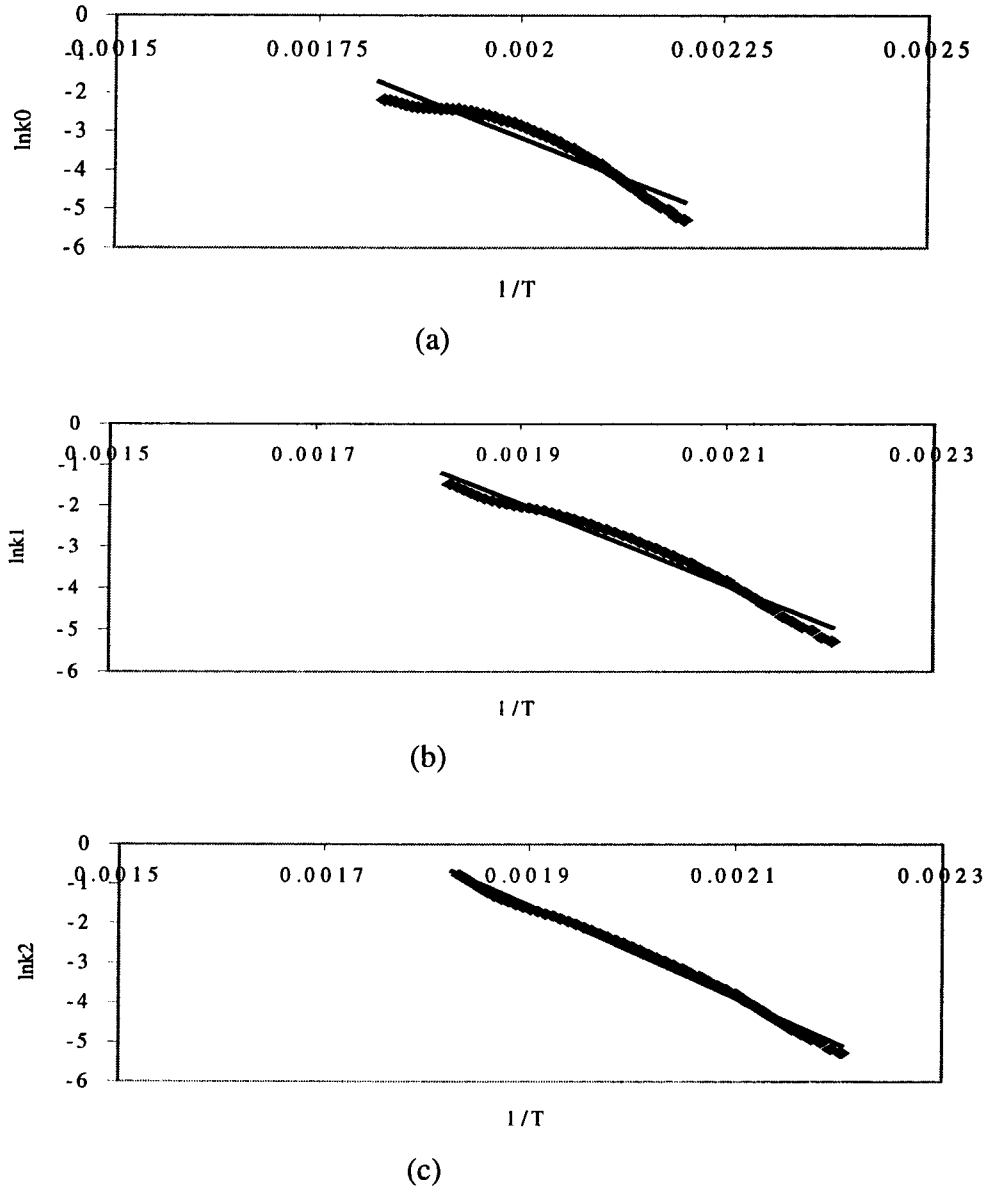

Fig. 8. Plot of the ln k against the reciprocal of temperature $1/T$ for captopril from the data obtained under the experimental conditions of 10°C min dry nitrogen 100 ml min^{-1}, sample weight of 10.56 mg using the Arrhenius equation assuming the (a) zero order where $R^2 = 0.9211$, slope $= -8180.7$ and an intercept of 13.195; (b) first order where $R^2 = 0.9718$, slope $= -9907.1$ and an intercept of 16.867; (c) second-order reactions where $R^2 = 0.9921$, slope $= -11634$ and an intercept of 20.538. (Plot for the data range from 181 to 273°C under the assumption of $\%W_i = 100$ and $\%W_f = 0\%$.)

3.2.4. Freeman and Carroll method

Two data ranges, namely $T_{i(ext)}$–T_{p1} and T_{p1}–T_{p2}, from the DTG curves are used for further kinetic analysis by the Freeman and Carroll method instead of one plot from the whole data range $T_{i(ext)}$–T_{p2}. This type of phenomena can also be seen in the kinetic analysis for captopril using the Arrhenius method. The only other difference selected for kinetic analysis

Table 3
Kinetic parameters from the Arrhenius plot for captopril using the assumptions of $\%W_i = 100\%$ and $\%W_f = \%W$ at T_t to obtained a better fit plot for each sample size from (a) first data range and (b) second data range (heating rate of 10°C min^{-1}, flow rate of 100 ml min^{-1} dry nitrogen)

Sample weight (mg)	Data range (°C)	Assumed order reaction	E_{act} (kJ mol^{-1})	Ln A	R^2
(a) *First data range*					
5.6892	181–251	2	109.0	24.3	0.9997
7.8635	181–253	2	107.4	23.7	1.0000
8.2930	177–261	2	108.0	23.8	0.9990
10.5735	181–253	2	107.6	23.5	0.9966
12.1731	181–253	2	108.7	23.7	0.9960
13.9414	181–255	2	108.8	23.7	0.9950
15.9774	181–255	2	108.8	23.7	0.9954
(b) *Second data range*					
2.7150	181–245	1	94.3	20.8	0.9992
7.8635	267–273	1	117.7	25.2	0.9997
8.2930	267–273	1	114.3	24.4	0.9998
10.5735	267–273	1	119.4	25.3	0.9994
12.1731	269–277	1	117.3	24.9	0.9998
13.9414	269–277	1	123.9	26.2	0.9994
15.9774	269–279	1	115.5	24.4	0.9992

between the Arrhenius and the Freeman and Carroll methods concerns the selection of the initial point. The weight at $T_{i(ext)}$ may be selected instead of the weight at T_i. The reason for this is that the Freeman and Carroll method is more sensitive to temperatures and the data range used in such calculations. This means that the beginning of the reaction would show more scatters in such plots.

The results from these plots using the Freeman and Carroll method are organized over a range between the

Table 4
Kinetic parameters from the Arrhenius plot for captopril using the assumptions of $\%W_i = 100\%$ and $\%W_f = \%W$ at T_t to obtained a better fit plot for each heating rate from (a) first data range and (b) second data range (flow rate of 100 ml min^{-1} dry nitrogen)

Heating rate (°C min^{-1})	Data range (°C)	Assumed order reaction	E_{act} (kJ mol^{-1})	Ln A	R^2
(a) *First data range*					
2	151–239	2	91.4	19.3	0.9974
4	159–247	2	101.0	21.9	0.9917
6	169–251	2	103.0	22.4	0.9872
8	179–255	2	103.7	22.5	0.9982
10	181–253	2	107.6	23.5	0.9966
12	195–267	2	104.8	22.4	0.9801
(b) *Second data range*					
2	243–255	1	113.8	23.7	0.9787
4	255–261	1	112.0	23.6	0.9981
6	259–267	1	109.9	23.2	0.9998
8	265–273	1	130.7	27.8	0.9991
10	267–273	1	119.4	25.3	0.9994
12	279–283	1	178.4	37.8	0.9746

Table 5
Kinetic parameters from the Freeman and Carroll method for captopril using the assumptions of $\%W_i = 100\%$ and $\%W_f = \%W$ at T_t to obtained a better fit plot for each sample size from (a) first data range and (b) second data range (heating rate of 10°C min^{-1}, flow rate of 100 ml min^{-1} dry nitrogen)

Sample weight (mg)	Data range (°C)	$\%W_i - \%W_f$ (range)	E_{act} (kJ mol^{-1})	nth order	R^2
(a) *First data range*					
2.7150	211–245	10–100%	101.0	1.3	0.9989
5.6892	217–261	19–100%	103.4	1.7	0.9950
7.8635	217–253	19–100%	108.0	2.1	0.9984
8.2930	221–261	17–100%	103.0	1.8	0.9900
10.5735	225–253	20–100%	106.4	2.3	0.9946
12.1731	231–253	18–100%	109.1	2.4	0.9742
13.9414	225–255	21–100%	108.1	2.4	0.9915
15.9774	231–255	21–100%	106.7	2.4	0.9785
(b) *Second data range*					
5.6892	265–273	19–100%	48.7	0.5	0.9652
7.8635	267–273	19–100%	73.9	0.6	0.8778
8.2930	267–273	17–100%	91.5	0.7	0.8942
10.5735	267–275	20–100%	101.4	0.7	0.9575
12.1731	269–277	18–100%	149.1	1.2	0.9792
13.9414	269–277	21–100%	152.6	1.2	0.9652
15.9774	269–279	21–100%	153.7	1.3	0.9826

initial and final weight. The activation energy E_{act}, order of reaction n and linear regression R^2 values are also reported in the tables.

3.2.4.1. Effect of various sample weights. The values for the activation energy E_{act}, order of reaction n and linear regression R^2 based on the Freeman and Carroll method for various sample weights are given in Table 5. This shows a first-order decomposition reaction at a sample weight of 2.7 mg. The second-order decomposition reaction is more dominate at a sample weight of 5.6 mg. In addition, the results show

Table 6
Kinetic parameters from the Freeman and Carroll method for captopril using the assumptions of $\%W_i = 100\%$ and $\%W_f = \%W$ at T_t to obtained a better fit plot for each different heating rates from (a) first data range and (b) second data range (flow rate of 100 ml min^{-1} dry nitrogen)

Heating rate (°C min^{-1})	Data range (°C)	$\%W_i - \%W_f$ (range)	E_{act} (kJ mol^{-1})	nth order	R^2
(a) *First data range*					
2	191–239	16–100%	91.0	2.1	0.9464
4	201–247	18–100%	93.5	1.9	0.9869
6	211–251	17–100%	97.7	2.0	0.9893
8	223–255	20–100%	144.5[a]	3.3[a]	0.4654[a]
10	225–253	20–100%	106.4	2.3	0.9946
12	233–267	21–100%	144.9[a]	35[a]	0.4345[a]
(b) *Second data range*					
2	243–255	16–100%	221.7[a]	1.9[a]	0.4866[a]
4	255–261	18–100%	129.6	1.1	0.9212
6	259–267	17–100%	112.1	1.0	0.9308
8	265–273	20–100%	143.6	1.1	0.8635
10	267–273	20–100%	101.4	0.7	0.9575
12	279–283	20–100%	418.4[a]	3.8[a]	0.4878[a]

[a] Does not give the good linear relationship on the curve of this results.

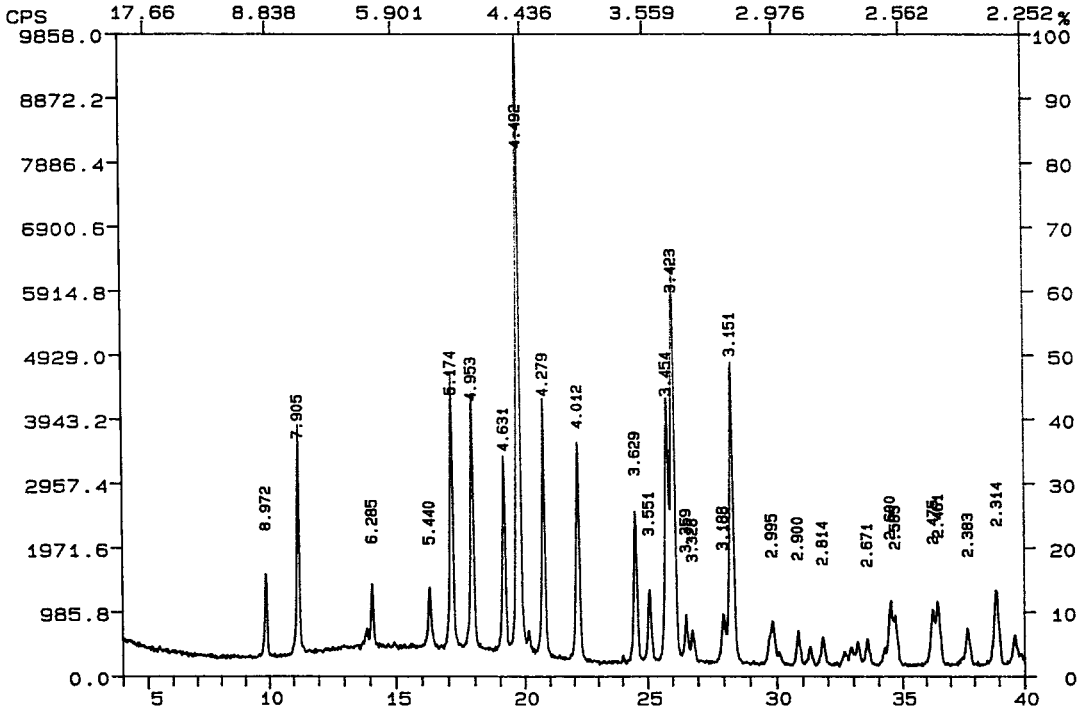

Fig. 9. The infrared spectrum of captopril in a KBr pellet obtained using the Nicolet 5.1 Instrument.

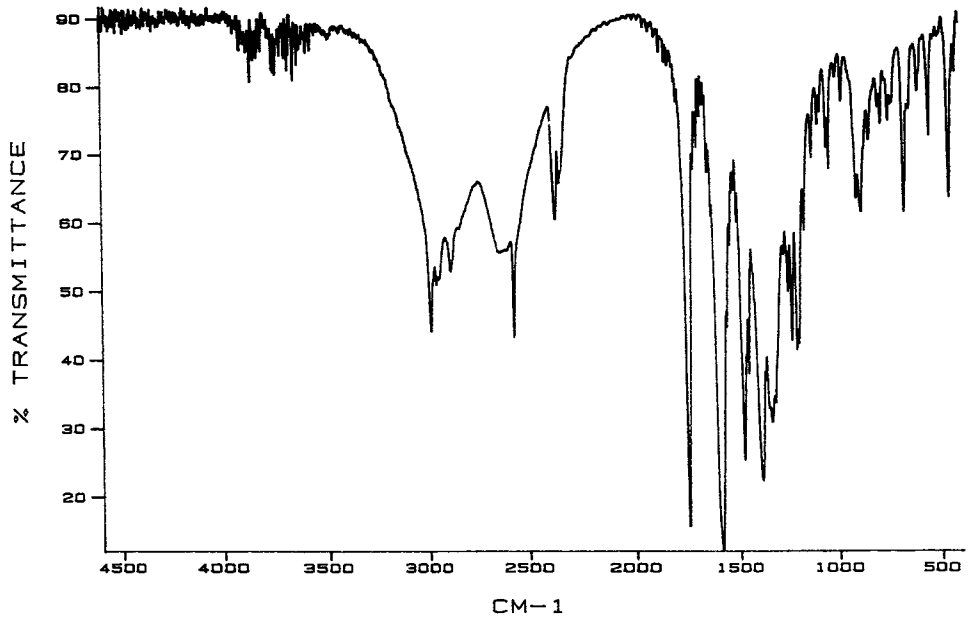

Fig. 10. The experimental X-ray diffraction graph for captopril obtained using the Scintag XDS 2000 Instrument.

that a second-order reaction mechanism for the first decomposition process is followed by a first-order reaction mechanism for the second decomposition process at sample weights above 5.6 mg. The activation energy for the second decomposition process was influenced by the initial sample weights. Activation energies for the first decomposition process shows less dependence on the initial sample weights. The activation energy for the first decomposition reaction is between 101.0 and 109.1 kJ mol^{-1} with the *n*th order range from 1.3 to 2.4. The activation energy for the second step decomposition reaction is between 94.3 and 123.9 kJ mol^{-1} with the *n*th order range from 0.5 to 1.3.

3.2.4.2. Effect of various heating rates. The values for the activation energy E_{act}, order of reaction n and linear regression R^2 based on the Freeman and Carroll method for various sample weights are given in Table 6. To compare the linear regression values

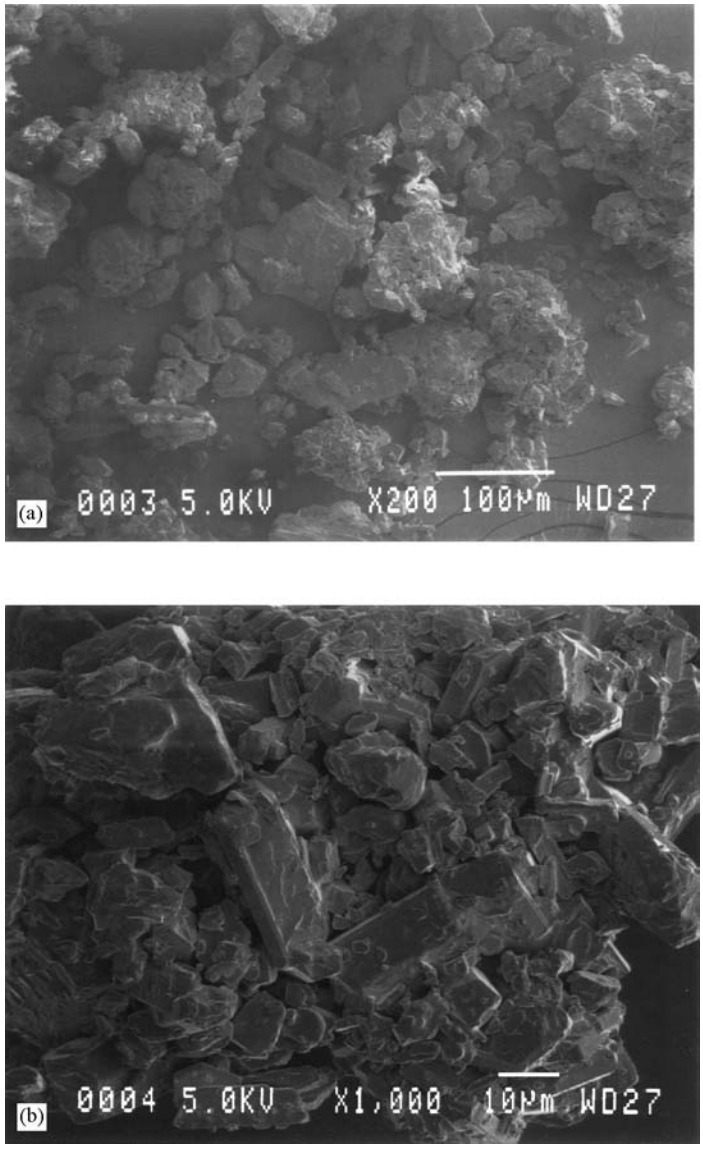

Fig. 11. SEM pictures for captopril: (a) magnification: 200×; (b) magnification: 1000×.

from various heating rates, it should be noted that good R^2 values can be obtained from different data range assumptions. The overall R^2 values are at least equal to 0.90 at the heating rate ranges 4–10°C min^{-1}. The conclusions drawn from data obtained for various heating rates is the assumption that the initial decomposition process is a second-order reaction followed by a first-order reaction (see Table 6(b)) because it provides a poorer experimental fit. This table shows that the various heating rates effect the activation energy obtained for captopril. The extremely low heating rate and the high heating rate do not provide enough data that can be interpreted in terms of a kinetic analysis. This suggests that the experimental heating rates used for captopril would be between 4 and 10°C min^{-1}. With this reasonable experimental heating rate range, the activation energy for the first-step decomposition reaction is between 91.0 and 106.4 kJ mol^{-1} with the *n*th order range from 1.9 to 2.3. The activation energy for the second-step decomposition reaction is between 101.4 and 143.6 kJ mol^{-1} with the *n*th order range from 0.7 to 1.1.

3.3. Supplemental experiments

The infrared spectrum of captopril in a KBr pellet (Fig. 9) presents the following frequencies 1750 and 2560 cm^{-1} which identify the functional groups as COOH group and SH group in the captopril structure. The experimental XRD pattern (Fig. 10) for captopril matches the database library patterns which are attached to the computer program. This conformation shows that the material used in this study is the stable form of captopril. The SEM pictures (Fig. 11) shows the solid state appearance of captopril. The particle sizes are varied from 10 to 30 μm in length along one side of the crystal. These particles may form an aggregate having approximately 100 μm diameters.

4. Conclusion

The supplemental experiments confirm that the material obtained for this study is captopril. Captopril melts at 106°C and this is then followed by decomposition. Captopril alone was shown to decompose in 2–3 steps depending upon the experimental conditions. From the isothermal results, captopril was decomposed as a second-order reaction at the lower temperature (180°C) and decomposed as a first-order reaction at the higher temperature (260°C). These results matched the results obtained from the rising temperature experiments. The kinetic analysis using the Arrhenius and the Freeman and Carroll methods show that captopril decomposes by a second-order reaction followed by a first-order reaction after heat treatment under a dry nitrogen atmosphere.

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