Eudragit E Accelerated the Diketopiperazine Formation of Enalapril Maleate Determined by Thermal FTIR Microspectroscopic Technique

Shun-Li Wang,[1] Shan-Yang Lin,[2,3] Ting-Fang Chen,[2] and Wen-Ting Cheng[2]

Received April 23, 2004; accepted July 15, 2004

Purpose. Enalapril may undergo the thermal-induced intramolecular interaction to cause an enalapril diketopiperazine (DKP) formation. It is interesting to study the influence of Eudragit E, as a coating polymer, on the stability of enalapril maleate. The reaction kinetics of the solid-state degradation process of pure enalapril maleate and Eudragit E/enalapril maleate mixture with different weight ratios were examined. The mechanism of solid-state interaction between Eudragit E and enalapril maleate was also discussed.

Methods. The cast samples of pure enalapril maleate or Eudragit E/enalapril maleate mixture after evaporating the solvent were prepared on an aluminum foil and also determined by reflectance Fourier transform infrared (FTIR) microspectroscopy equipped with thermal analyzer.

Results. The result indicates that the interaction might occur between enalapril maleate and Eudragit E in the solid state after evaporating the solvent. The thermal-dependent FTIR spectra show that not only the formation of DKP but also the six-membered cyclic anhydride occurred in the enalapril maleate/Eudragit E mixture in the heating process. Two pathways for solid-sate interaction were proposed. The stability of enalapril maleate was dependent on the weight ratio of enalapril maleate and Eudragit E. The activation energy (n = 3) of DKP formation for pure enalapril maleate was about 141.2 ± 0.7 kJ/mol, but it was reduced significantly to 86.7 ± 0.8 kJ/mol after interaction with Eudragit E (weight ratio: 1:1), suggesting Eudragit E might exacerbate the degradation of enalapril maleate. However, the degradation accelerated by Eudragit E was reduced in high content of Eudragit E.

Conclusions. When the weight ratio of both components was 1:1, Eudragit E might interact with the carboxyl group of maleic acid to exacerbate the degradation of enalapril maleate. However, the excess amount of Eudragit E might somewhat reduce the degradation of enalapril, due to the interaction that occurred between Eudragit E and carboxyl group of enalapril.

KEY WORDS: enalapril maleate; Eudragit E; solid-state interaction; stability; thermal FTIR; weight ratio; reaction pathway.

INTRODUCTION

Many polymers have extensively been used in the pharmaceutical industry to film-coat on the surface of tablets, pellets, granules, or beads for different purposes or to formulate with drug to control the release of drug. If the interaction occurs between polymer and drug, the physicochemical properties of drug and its release characteristics, as well as drug stability, may be changed (1–3). Two types of polymer-drug interaction may simply be classified: one is physicochemical interaction to change the solubility, phase transition, or polymorphic transformation of drugs; the other is chemical interaction to have acid-base reaction, hydrolysis, oxidation, polymerization, rearrangement, cyclization, and photochemical reaction (4). In particular, a drug after chemical interaction might lose its pharmacological activity and/or induce side effects (5–7).

Enalapril is a type of angiotensin-converting enzyme (ACE) inhibitor used to treat high blood pressure and heart failure. However, it is easily accelerated to form an enalapril diketopiperazine (DKP) via intramolecular cyclization in aqueous solution and solid state. The key step was the attack on the carboxylic group by the secondary amine within the enalapril structure via intramolecular aliphatic nucleophilic substitution reaction (8–9). To prevent the formation of DKP, a potential carcinogen (10–11), enalapril is commercialized as a maleate salt to reduce the attacking ability of the nitrogen atom in its amine group.

Eudragit E is a cationic copolymer of *N,N*-dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It has often been used as a coating film to mask the unpleasant tastes and odors of drugs, as well as to protect drugs against moisture for pharmaceutical applications (12). Because Eudragit E possesses a basic site of dimethylamino group, it can easily dissolve in gastric juice even as a coating film. However, the thermal-induced formation of six-membered cyclic anhydride was evidenced in Eudragit E film by intramolecular ester condensation in the heating process (13).

A novel and powerful Fourier transform infrared (FTIR) microspectroscope equipped with a thermal analyzer has been used to study the solid-state intramolecular cyclization of drugs or polymers, such as aspartame, enalapril, lisinopril, or methacrylic acid copolymers (Eudragit E & L) (9,13–17). However, these investigations were only focused on one thermal-dependent reactant. What is the fate of two reactants (enalapril and Eudragit E) that coexisted in the system in the heating process? It is interesting to know whether Eudragit E will influence the stability of enalapril maleate when enalapril maleate and Eudragit E are formulated together. Thus, in this study, the thermal FTIR system was applied to investigate the mutual interaction between enalapril maleate and Eudragit E.

MATERIALS AND METHODS

Materials

Enalapril maleate used in this study was of pharmaceutical grade and was purchased from Chem. Works Gedeon Richter Ltd. (Budapest, Hungary). Eudragit E-100 [copolymer of butyl methacrylate, 2-dimethylaminoethyl methacrylate, and methyl methacrylate (1:2:1); molecular weight 150,000] was kindly supplied by Rohm Pharm (Darmstadt, Germany). Aluminum foil was purchased from Reynolds Metals (Richmond, Virginia, USA). The reagent grade of an-

[1] Department of Applied Chemistry, National ChiaYi University, ChiaYi, 600, Taiwan, Republic of China.

[2] Biopharmaceutics Laboratory, Department of Medical Research and Education, Veterans General Hospital-Taipei, Shih-Pai, 11217, Taipei, Taiwan, Republic of China.

[3] To whom correspondence should be addressed. (e-mail: sylin@vghtpe.gov.tw)

hydrous ethanol (99.9%) and the KBr crystal for pellet were obtained from Nakalai Tesque (Kyoto, Japan).

Preparation of Sample Cast on Aluminum Foil

Different weight ratios (1:1, 1:2, and 1:3 w/w) of enalapril maleate/Eudragit E mixture were mixed and then dissolved in ethanol solution. Pure enalapril maleate or Eudragit E was also respectively dissolved in ethanol solution. These ethanolic solutions were respectively cast on an aluminum foil. All samples cast were dried at 30°C for 1 week and tested by FTIR spectra to show no solvent absorption.

Reflectance Thermal-FTIR Microspectroscopic Study

The sample cast on aluminum foil was carefully cut to 6 mm × 6 mm in size. This foil was put directly on a micro hot stage (DSC microscopy cell, FP 84, Mettler, Greifensee, Switzerland). The DSC microscopy cell was then placed on the stage of the microscope in the FTIR microspectrometer (Micro FTIR-200, Jasco, Tokyo, Japan) with an MCT detector. The temperature of the DSC microscopy cell was monitored with a central processor (FT80HT, Mettler). The temperature of the FTIR microscopy cell was calibrated with indium. The polystyrene film was used as a wave number calibrator of FTIR microscopic spectrometer. The heating rate was controlled at 3°C /min. The FTIR was operated in the reflectance mode and performed from 30°C to 300°C. The reflectance IR spectra were collected at an angle of incidence centered at 30° taken with a resolution of 4 cm^{-1}. Generally, 20 scans, after subtracting out an air blank, were accumulated to get a reasonable signal to noise ratio. The level of signal vs. noise was 5000:1.

RESULTS AND DISCUSSION

Solid-State Interaction Between Enalapril Maleate and Eudragit E

The reflectance FTIR spectra for the cast samples of enalapril maleate, Eudragit E, and their mixture (weight ratio 1:1) at room temperature are displayed in Fig. 1. The assignment of FTIR absorption band of enalapril maleate and Eudragit E are listed in Table I. However, the IR spectra of sample cast of enalapril maleate/Eudragit E mixture (weight ratio 1:1) clearly indicate the disappearance of the absorption band at 2821, 2771 cm^{-1} (belonging to N,N-dimethyl group of Eudragit E), and 1221 cm^{-1} (belonging to C–C–O group of enalapril maleate). It has been reported that the IR spectra of the basic site containing the $N(CH_3)_2$ group exhibited a medium to strong peak intensity within 2760–2820 cm^{-1} and might act as a valuable and special diagnostic group (18–19). Any structural modifications that involved the lone pair of nitrogen electrons, such as protonation, might cause the disappearance of this absorption band. Therefore, it is reasonable to predict the interaction between enalapril maleate and Eudragit E to be an acid-base reaction in the solid state to make the disappearance of N,N-dimethyl group and carboxyl group.

In order to explore the influence of temperature on the polymer-drug interaction, the three-dimensional plots of FTIR spectra of enalapril maleate/Eudragit E mixture (weight ratio 1:1) as a function of temperature are shown in Fig. 2. Following Le Chatelier's principle (20), the equilibrium of acid-base reaction might dissociate with the increase of temperature, so that the peak intensity at 2821 and 2771 cm^{-1} might slightly increase. But beyond 106°C, these peak intensities darmatically enhanced, then disappeared at high

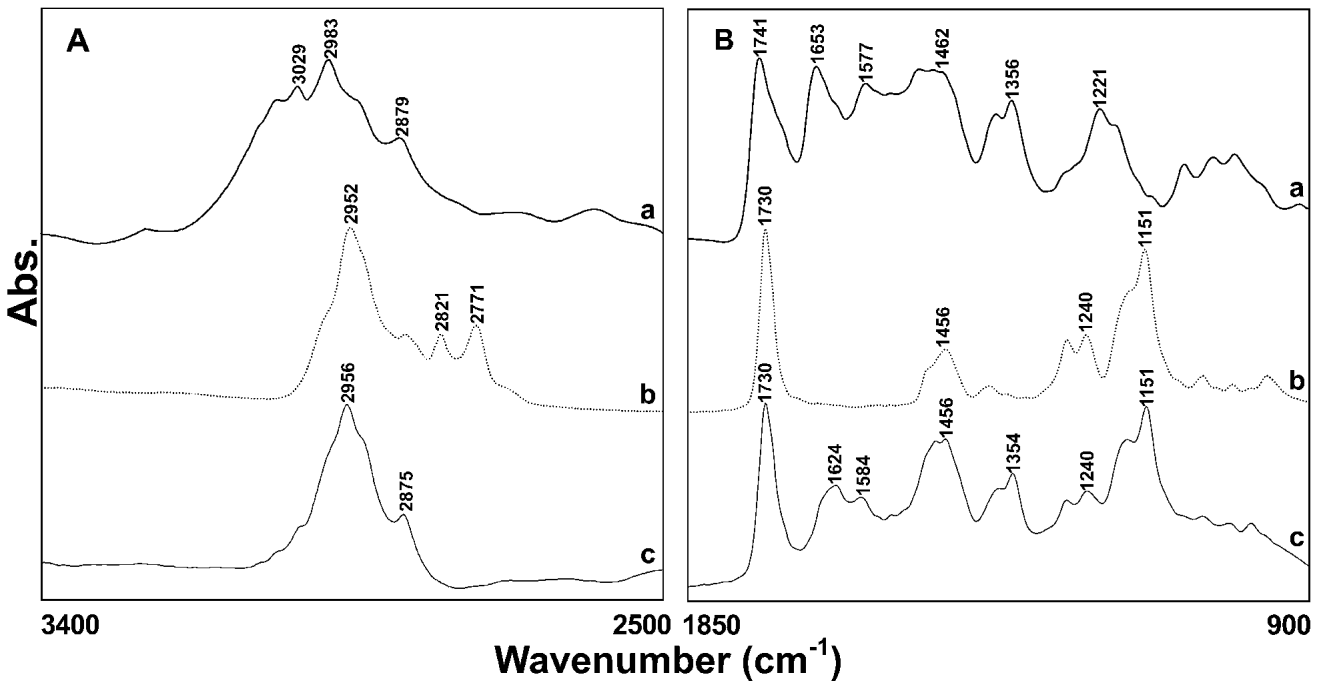


Fig. 1. The reflectance FTIR spectra for the casted samples of enalapril maleate (a), Eudragit E (b), and enalapril maleate/Eudragit E mixture (weight ratio 1:1) (c) at room temperature. IR range for 3400–2500 cm-1 (A) and 1850–900 cm-1 (B).

Table I. The Assignment of FTIR Absorption Band on Fig. 1

	Position (cm^{-1})	Assignment
Enalapril maleate (Fig. 1a)		
	3029	Unsaturated C–H stretching
	2983	Asymmetric C–H stretching
	2879	Symmetric C–H stretching
	1741	C = O stretching of ester
	1653	C = O stretching of tertiary amide
	1577	Asymmetric carboxylate
	1462	C–H bending
	1356	C–H bending/symmetric carboxylate
	1221	C–C–O stretching of acetate and ester
Eudragit E100 (Fig. 1b)		
	2952	Asymmetric C–H stretching
	2821 and 2771	C–H stretching of dimethylamino group
	1730	C = O stretching of ester
	1456	C–H bending
	1240	C–O stretching of ester
	1151	C–N stretching

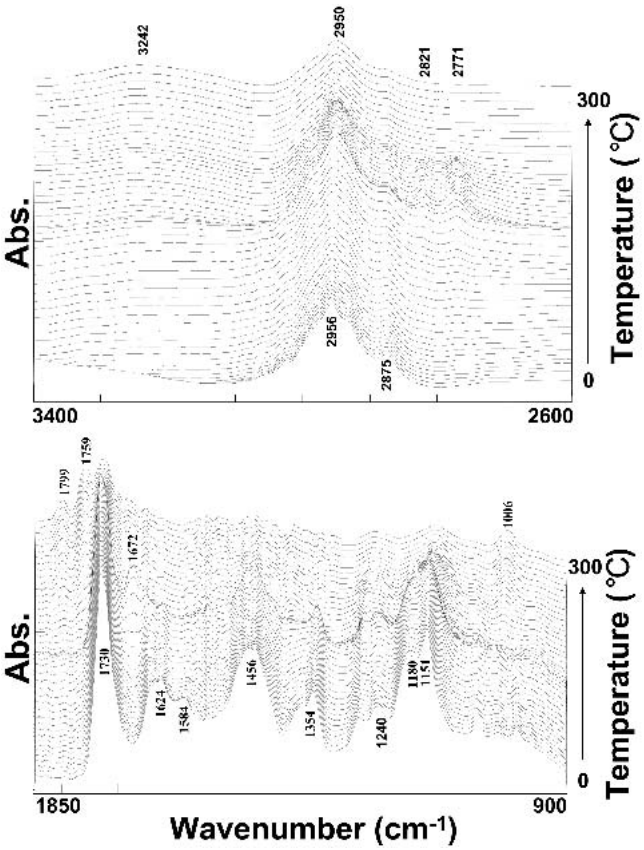


Fig. 2. Three-dimensional plots of FTIR spectra for the sample cast of enalapril maleate/Eudragit E mixture (weight ratio 1:1) as a function of temperature. IR range for 3400–2500 cm-1 (upper) and 1850–900 cm-1 (lower).

temperature. Our previous study has proven that the DKP might be formed by heating a solid-state enalapril maleate, as the carbonyl band of DKP might appear at 1672 cm^{-1} due to intramolecular cyclization in enalapril maleate (9,16). Eudragit E was also found to form six-member cyclic anhydrides via intramolecular ester condensation, due to the appearance of the anhydride-related IR spectra at 1801, 1763, and 1007 cm^{-1} at high temperature (13). In this study, several IR peaks at 1799, 1759, 1672, and 1006 cm^{-1} found in the thermal-dependent three-dimensional plots of FTIR spectra indicate that not only the formation of DKP but also the six-member cyclic anhydrides occurred in the enalapril maleate/Eudragit E mixture in the heating process.

The temperature-dependent changes in peak intensity of several IR bands for the cast samples of enalapril maleate, Eudragit E, and their mixture (weight ratio 1:1) are shown in Fig. 3A. DKP formed at 1672 cm^{-1} (the carbonyl band of DKP) in pure enalapril maleate at temperature beyond 129°C. However, it formed at lower temperature of 106°C in the sample cast of enalapril maleate/Eudragit E mixture. Furthermore, the IR band at 2771 cm^{-1} for N,N-dimethyl group of Eudragit E in the sample cast of enalapril maleate/Eudragit E mixture increased gradually at the initial heating stage but enhanced dramatically when temperature went over 150°C. The peak intensity of 2771 cm^{-1} reached maxima at 185°C and then decreased with temperature. The temperature at 185°C was also the onset temperature for the formation of six-member cyclic anhydrides, due to the appearance of 1006 cm^{-1}. However, the increasing phenomenon for IR peak at 2771 cm^{-1} was not observed in the pure Eudragit E in the heating process. Oppositely, the peak intensity of 2771 cm^{-1} of pure Eudragit E decreased with temperature via intramolecular ester condensation.

There are two acidic sites on maleic acid, its dissociation constant (pK_a) to be 1.83 and 6.07, respectively (21). After complex with enalapril, enalapril maleate has two acidic sites (pK_{a1} = 3.0 and pK_{a2} = 5.4), one site is on enalapril molecule and the other one is on maleic acid. The disappearance of the N,N-dimethyl group at 2821 and 2771 cm^{-1} (Fig. 1) suggested the formation of acid-base complex between enalapril maleate and Eudragit E in the solid state after evaporation of ethanol. There are two possible pathways for the interaction between enalapril maleate and Eudragit E, as proposed in Scheme 1. If Eudragit E interacts with one carboxyl group of maleic acid (A pathway), the interaction between maleic acid and enalapril will be weakened by increasing the electron density on maleic acid (22). In this pathway, the N atom of amine group on enalapril will become free after interacting with Eudragit E, and the degradation of enalapril through DKP formation would become easier. On the other hand, the interaction between Eudragit E and carboxyl group of enalapril (B pathway) will increase the electron density of the carbon atom in the carboxyl group. Therefore, the formation of DKP through the attack of amine group is unfavorable, because the electrophility of carbon atom on carboxyl group will increase (22). The degradation of enalapril through DKP formation is proposed to become harder after interacting with Eudragit E if the interaction is through B pathway. Because the onset temperature of DKP formation for enalapril maleate after interacting with Eudragit E shifted from 129°C to 106°C, pathway A was supposed to explain the mechanism for

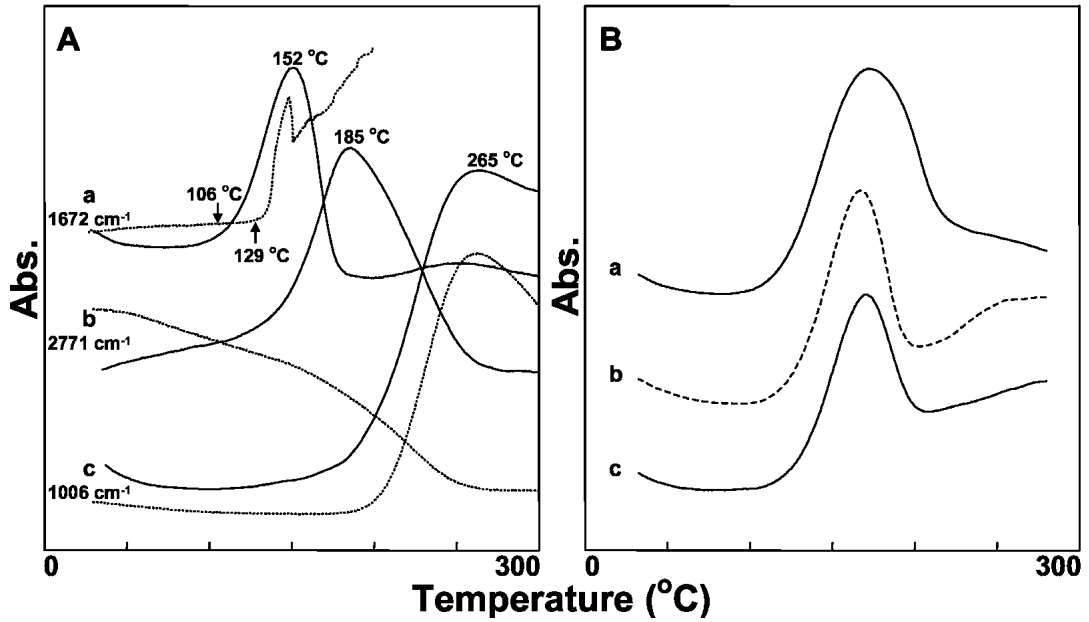


Fig. 3. Temperature-dependent changes in peak intensity of several IR bands for the casted samples of enalapril maleate (a, dotted line), Eudragit E (b and c, dotted lines), and their mixture in weight ratio 1:1 (solid lines) (A) and in IR spectral band at 1672 cm^{-1} for different weight ratios (a, 1:1; b, 1:2; c, 1:3) of enalapril maleate/Eudragit E mixture (B).

that interaction when the weight ratio of the enalapril maleate/Eudragit E mixture is 1:1 (Scheme 2). The temperature-dependent changes in IR spectral band at 1672 cm^{-1} for different weight ratios of enalapril maleate/Eudragit E mixture are shown in Fig. 3B. Obviously, the weight ratio of 1:1 displayed a wider band than other weight ratios, implying that the formation of DKP was less sensitive to temperature change (23).

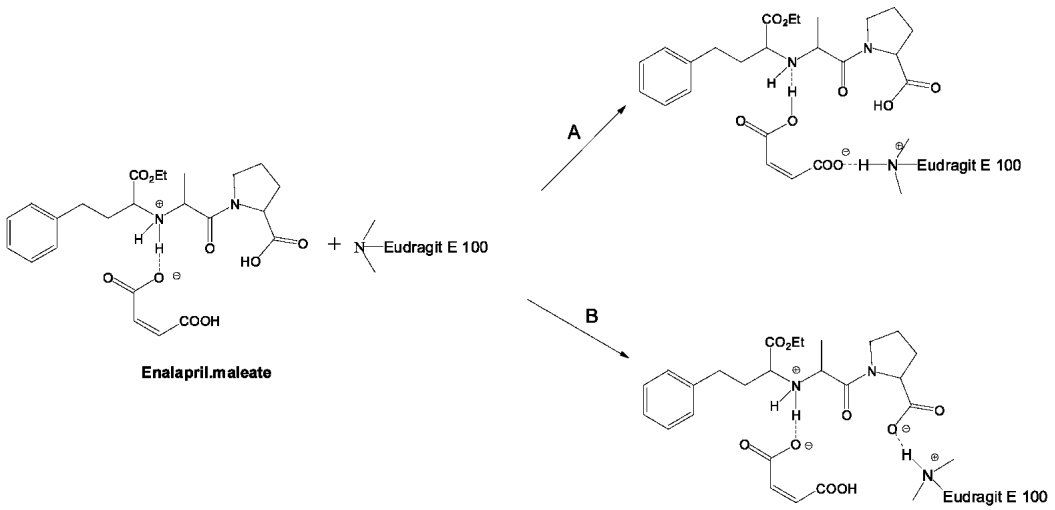
Kinetic Study of Degradation of Pure Enalapril Maleate in Different Weight Ratios of Enalapril Maleate/Eudragit E Mixture

To quantify the kinetic parameters of the DKP formation of enalapril maleate in pure enalapril maleate and different weight ratios of enalapril maleate/Eudragit E mixture, the non-isothermal heating condition was applied to study the solid-state reaction kinetics. The appearance of 1672 cm^{-1} was used as a reference to determine the fraction decomposed, α, which can be expressed by

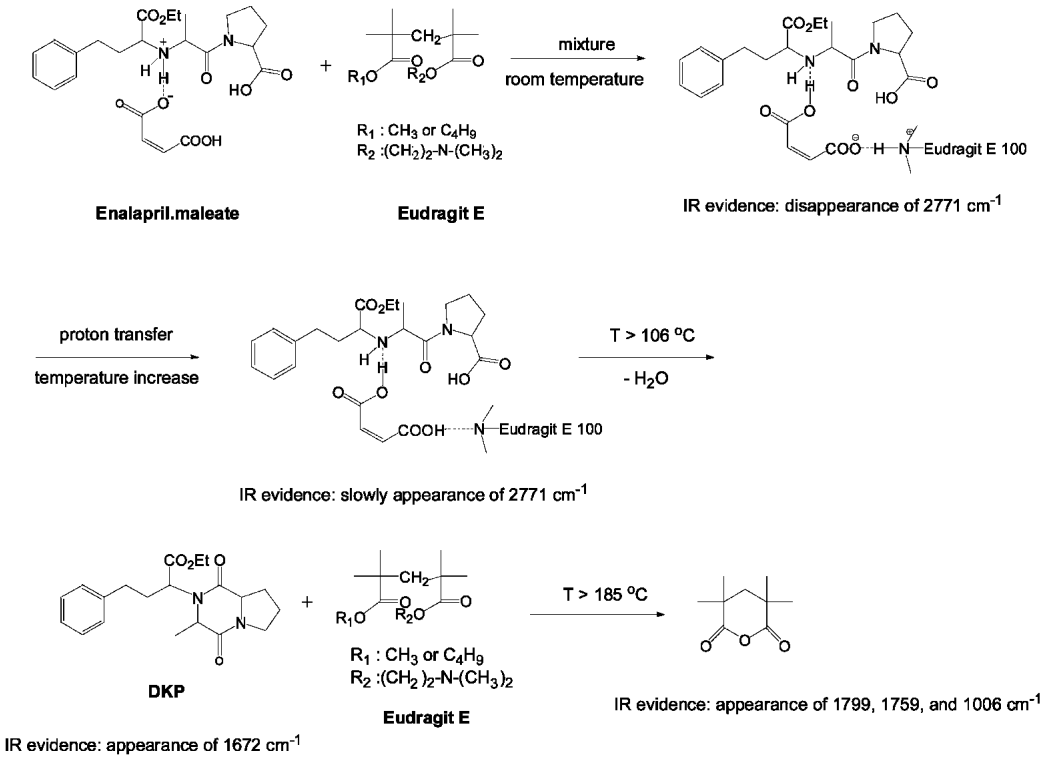
$$\alpha = \frac{I_{(t)}}{I_{max}} \tag{1}$$

where $I_{(t)}$ is the peak intensity at 1672 cm^{-1} at time t, and I_{max} is the maximum peak intensity at 1672 cm^{-1} in the heating process. The derivative of α to time was fitted to several non-isothermal kinetic equations. The best-fitted equation determined by the least squares analysis is the first-order kinetic equation as follows:

$$\frac{d\alpha}{dt} = k_T(1-\alpha) \tag{2}$$



Scheme 1. The possible pathways for the interaction between enalapril maleate and Eudragit E in the solid state.



Scheme 2. The proposed pathways for the solid-sate interaction between enalapril maleate and Eudragit E in the heating process.

where k_T is the reaction rate constant at temperature T and t is time. The activation energy (E_a) of the decomposition for enalapril maleate is determined by an Arrhenius equation as follows:

$$k_T = A \exp(-E_a/RT) \quad (3)$$

where A is a frequency factor, and R is the gas constant. A plot of ln k_T obtained from the first-order equation (Eq. 2) against *I/T* is shown in Fig. 4. Because DKP will decompose at high temperature, the kinetic parameter was calculated when the value of α was between 5% and 80%. The kinetic parameters (n = 3) of the decomposition for pure enalapril maleate and various weight ratios of enalapril maleate/ Eudragit E mixture are listed in Table II.

The activation energy of DKP formation for pure enalapril maleate (cast on aluminum foil) was about 141.2 ± 0.7 kJ/mol (16), but the activation energy of DKP formation for enalapril maleate after interaction with Eudragit E (weight ratio 1:1) seemed to reduce significantly to 86.7 ± 0.8 kJ/mol. In other words, the Eudragit E might exacerbate the degradation of enalapril maleate. However, it is interesting to note that when the weight ratio of Eudragit E went over 1:2 in the enalapril maleate/Eudragit E mixture, the activation energy of DKP formation markedly increased again. Once the amount of Eudragit E in the weight ratio of enalapril maleate/ Eudragit E mixture was increased, the excess of Eudragit E molecules was supposed to interact with the carboxyl group of enalapril molecule (B pathway in Scheme 1). Here, one can expect that the electron density in the carboxyl group of enalapril will increase, to weaken the degradation of enalapril and enhance the stability of enalapril in enalapril maleate/ Eudragit E mixture with a high ratio of Eudragit E. Because the acid strength of the secondary acidic site on enalapril maleate is weak, the acid-base interaction is also weak on this site. Therefore, the stability of enalapril maleate can only slightly increase with more Eudragit E in enalapril maleate/ Eudragit E mixture.

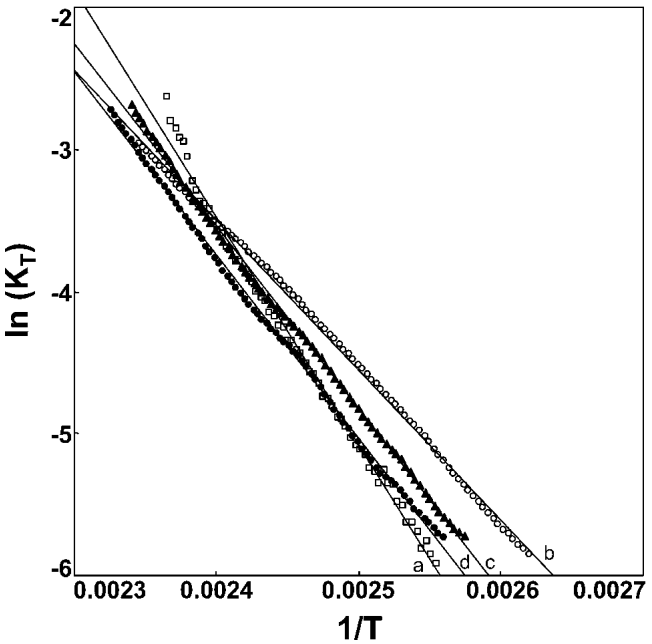


Fig. 4. A plot of ln k_T against 1/T for thermal decomposition of different weight ratios of enalapril maleate/Eudragit E mixtures. Key: (a) pure enalapril maleate (□); weight ratio of enalapril maleate/ Eudragit E mixture: (b) 1:1 (○); (c) 1:2 (▲); (d) 1:3 (●).

Table II. Kinetic Parameters for the Decomposition of Enalapril Maleate in Various Ratios of the Casted Sample of Enalapril Maleate/Eudragit E Mixture

Parameters/Samples	Pure enalapril maleate	Eudragit E-100/enalapril maleate		
		1:1	2:1	3:1
Activation energy (kJ/mol)	141.2 ± 0.7[a]	86.7 ± 0.8	113.0 ± 2.3	109.9 ± 2.8
Frequency factor (ln A)	37.3 ± 0.6	21.4 ± 0.3	28.9 ± 0.6	28.0 ± 0.6

[a] Mean ± standard deviation (n = 3).

CONCLUSIONS

The result of this study shows the solid-state interaction between enalapril maleate and Eudragit E after evaporating the solvent. This interaction might influence the stability of enalapril maleate, depending on the weight ratio of enalapril maleate and Eudragit E. When the weight ratio is 1:1, Eudragit E may interact with the carboxyl group of maleic acid to exacerbate the degradation of enalapril maleate. When the weight ratio is in excess of Eudragit E, however, the degradation of enalapril may somewhat be reduced due to the interaction between Eudragit E and carboxyl group of enalapril.

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