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Formation of six-membered cyclic anhydrides by thermally induced intramolecular ester condensation in Eudragit E film

Shan-Yang Lin*, Hui-Ling Yu, Mei-Jane Li

Biopharmaceutics Laboratory, Department of Medical Research and Education, Veterans General Hospital–Taipei, Taipei, Taiwan

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Abstract

Eudragit E, a copolymer of *N*,*N*-dimethylaminoethyl methacrylate and neutral methacrylic acid esters, has been found to form six-membered cyclic anhydrides via intramolecular ester condensation by a heating process only, without adding any catalyst or initiator. A novel reflectance Fourier transform infrared microspectroscopy system equipped with differential scanning calorimetry (FTIR/DSC) was used to determine the thermal-dependent anhydride formation of Eudragit E film. The anhydride-related IR peaks at 1801, 1763 and 1007 cm^{-1} appeared from 180°C and increased with the heating temperature, while the peaks at 2820 and 2770 cm^{-1} for the dimethylamino group reduced gradually with the increase of temperature, strongly suggesting that the anhydride formation by ester condensation started above 180°C. The appearance of peaks at 1801 and 1763 cm^{-1} not only illustrates the asymmetric and symmetric stretching vibration mode of the carbonyl group existing in the anhydride structure, but also exhibits the formation of six-membered cyclic anhydrides during the heating process. Moreover, the higher peak intensity ratio of 1763 cm^{-1}/1801 cm^{-1} also reveals the predominant role of intramolecular ester condensation in anhydride formation in Eudragit E film. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Eudragit E; Anhydride formation; Ester condensation

1. Introduction

Eudragit E is a cationic copolymer of *N*,*N*-dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It becomes water-soluble by forming salts with acids, thus enabling film coating to dissolve in gastric juice. The film of Eudragit E has been used to mask unpleasant tastes and odours of drugs, as well as to protect drugs against moisture for pharmaceutical applications [1,2]. Lin and co-workers have investigated the mechanical properties, adhesion strength, drug–polymer interaction and drug release from a self-adhesive drug-loaded Eudragit E film for transdermal applications [3–6]. Our previous studies have found that the film of Eudragit L, an enteric-coating polymer constructed from a copolymer of methacrylic acid and methyl methacrylate, can easily form cyclic anhydrides within and/or between the polymer chains during the heating process [7–9]. Since the Eudragit L polymer contains many free carboxylic acids on the polymer chain in which the ratio of free carboxylic acids to the esters is about 1:1, the vicinal carboxylic acid groups and carboxylic ester groups in the Eudragit L polymer chain might be responsible for the anhydride formation. It has also been reported that the dicarboxylic acids certainly yield anhydrides through simple heating [10]. On the other hand, Eudragit E without free carboxylic groups only consists of three types of esters (the *N*,*N*-dimethylaminoethyl ester, methyl ester and butyl ester) on the polymer chain. The formation of anhydrides via only ester condensation by heat treatment seems to be an attractive investigation.

In our laboratory, a novel Fourier transform infrared microspectroscopy system equipped with differential scanning calorimetry (FTIR/DSC) was used to simultaneously investigate the correlation between the thermal treatment and the structural changes of drugs, fish oil, liquid crystal, skins and polymers by using a transmission method [11–15]. Reflectance FTIR/DSC microspectroscopy has been applied to determine the non-isothermal and isothermal kinetics of anhydride formation in Eudragit L film [7–9], and the changes in protein conformation of human pituitary adenomas [16]. This system offers a fast, simple, precise and reproducible operation to determine the thermal-dependent characteristics of samples. The purpose

* Corresponding author. Fax: +886-2-2875-1562; E-mail: sylin@isc1.vghtpe.gov.tw

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of this study was to investigate whether the thermally induced anhydride formation in the Eudragit E film takes place via ester condensation only due to the lack of carboxylic structure on the polymer chain and the absence of catalyst or initiator by using the reflectance FTIR/DSC microspectroscopic technique.

2. Experimental

2.1. Materials

Eudragit E-100 polymer (copolymer of butyl methacrylate, 2-dimethylaminoethyl methacrylate and methyl methacrylate (1:2:1), molecular weight 150 000) as a granule was kindly supplied by Rohm Pharma (Darmstadt, Germany). Aluminum foil was purchased from Reynolds Metals, (Virginia, USA). Anhydrous ethanol was a reagent grade, obtained from Nakalai Tesque (Kyoto, Japan).

2.2. Preparation of Eudragit E film coated on aluminum foil

A dilute Eudragit E solution (6% in anhydrous ethanol) was dropped onto the aluminum foil. A spin coater (SC-300, E.H.C., Taiwan, ROC) was used to prepare a uniform and smooth film of Eudragit E, which was then vacuum-dried at 60°C for 30 min. The thickness of the Eudragit E film coated on foil was about 8 μm.

2.3. Thermal analysis of Eudragit E samples

A certain amount of the ethanolic Eudragit E solution (6%) was filled into the DSC aluminum pan, and then the solvent was evaporated at room temperature. The sample in the DSC pan was then vacuum-dried for 12 h at 60°C and examined by differential scanning calorimetry (DSC-910, TA Instruments, USA) at a heating rate of 10°C min^{-1} with an open pan system in a stream of N_2 gas. The DSC cell was calibrated with indium. The granules and pulverized powders of Eudragit E were also examined as control. The 300°C-preheated samples were measured by reflectance FTIR microspectroscopy. Thermogravimetric analysis (TGA-951, Du Pont, USA) was also performed at the same heating rate.

2.4. Reflectance FTIR/DSC microspectroscopic study

The Eudragit E film coated on aluminum foil was carefully cut to 6 mm × 6 mm in size. This sample disc was inserted directly into the DSC microscopy cell (FP 84, Mettler, Switzerland). The DSC microscopy cell was then placed on the stage of the microscope in the FTIR microscopic spectrometer (Micro FTIR-200, Jasco, Japan) with an MCT detector. The system was operated in the reflectance mode, as described in our previous papers [7–9]. The temperature of the DSC microscopy cell was monitored with a central processor (FT80HT, Mettler, Switzerland). The heating rate of the DSC assembly was controlled at 10°C min^{-1}. This reflectance FTIR/DSC system was operated from 30 to 320°C, so that the thermal-related IR spectra could be recorded simultaneously. The reflectance IR spectra were collected at an angle of incidence centered at 30°C taken with a resolution of 4 cm^{-1}.

3. Results and discussion

Fig. 1 shows the temperature-dependent three-dimensional plots of the reflectance FTIR spectra of Eudragit E film at 3200–2600, 1850–1650 and 1350–900 cm^{-1}. Fig. 2 compares the FTIR spectra of the sample at 30 and 320°C. At the initial temperature (30°C), the peaks at 2955 and 2874 cm^{-1} were assigned to asymmetric and symmetric CH_3 groups of Eudragit E in the range between 3200 and 2600 cm^{-1}, and the peaks at 2820 and 2770 cm^{-1} were due to the dimethylamino groups of Eudragit E. In the range of 1900 and 900 cm^{-1}, the peak at 1730 cm^{-1} assigned to the carbonyl group, the peak at 1458 cm^{-1}

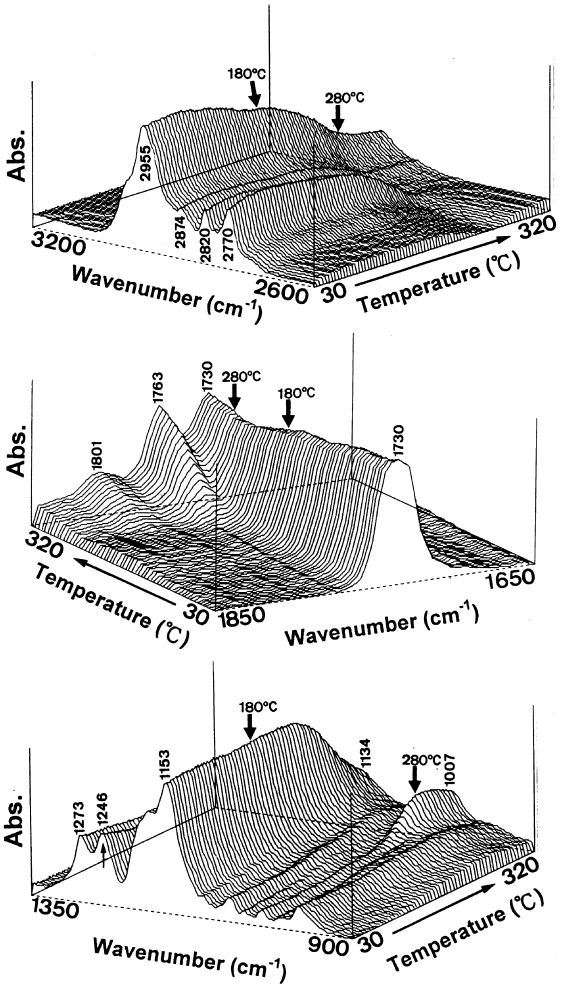

Fig. 1. Three-dimensional plots of reflectance FTIR spectra of Eudragit E film with respect to the temperature.

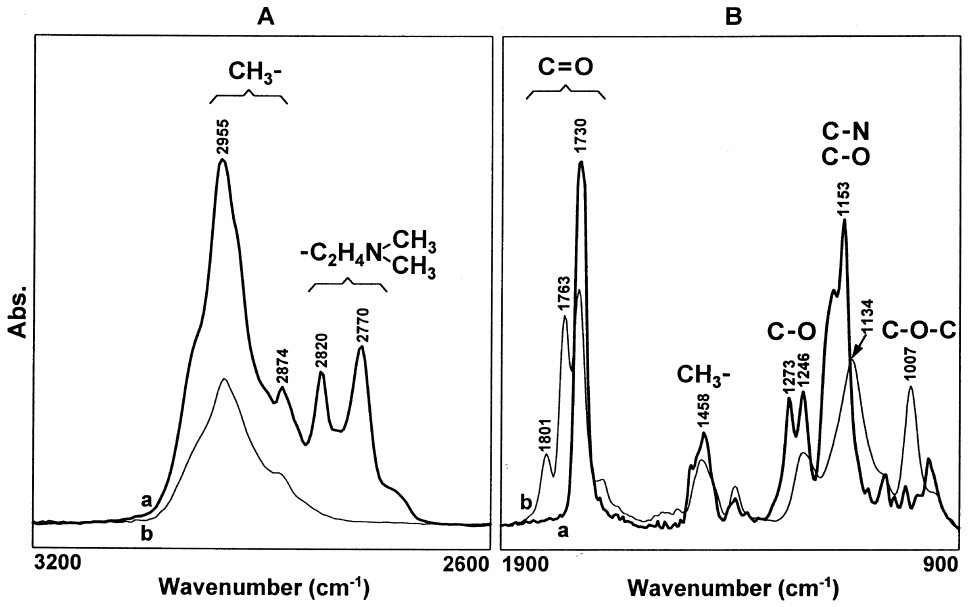

Fig. 2. Comparison of reflectance FTIR spectra of Eudragit E film samples heated at (A) 30°C and (B) 320°C.

corresponded to the C–H bending vibration for the methyl group, the peaks at 1273 and 1246 cm^{-1} were due to the C–O stretching vibration of the ester group, and the peak at 1153 cm^{-1} may be assigned to the C–N stretching absorption of aliphatic amines and/or the C–O stretching vibration of ester groups in Eudragit E [17,18], respectively. Apparently, the frequency and peak intensity of the reflectance FTIR spectra may change with increasing temperature. Once the Eudragit E film was heated beyond 180°C, the intensity of the peaks at 2820 and 2770 cm^{-1} assigned to the dimethylamino group of Eudragit E began to decrease with the increase of temperature. When the heating temperature reached 280°C, the intensity of both peaks seemed to flatten out, suggesting the complete loss of the dimethylaminoethyl group from the Eudragit E film. Two another specific bands at 1801 and 1763 cm^{-1} appeared from 180°C, and their peak intensities kept strengthening with an increase in temperature (Fig. 3). These new peaks at 1801 and 1763 cm^{-1} were assigned to asymmetric and symmetric stretching vibration of the carbonyl group in an anhydride, implying the formation of an anhydride in the Eudragit E film during the heating process [17–19]. Pretsch et al. [18] have pointed out the carbonyl stretching vibration of six-membered cyclic anhydrides at 1800 and 1760 cm^{-1}, rather than at 1850 and 1775 cm^{-1} for five-membered cyclic anhydrides, is indicative of the formation of six-membered

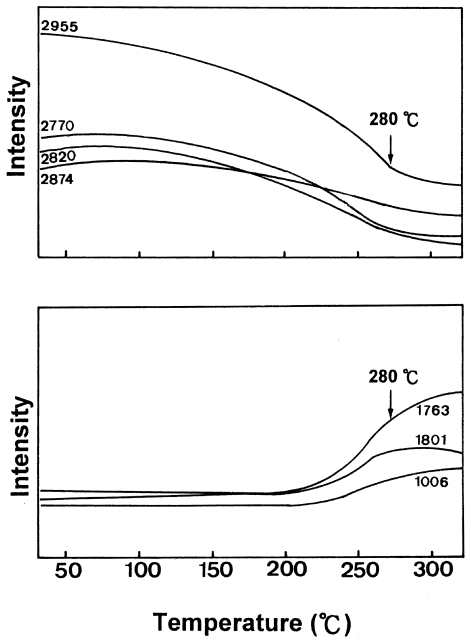

Fig. 3. Changes in intensity of representative peaks for anhydride formation with temperature.

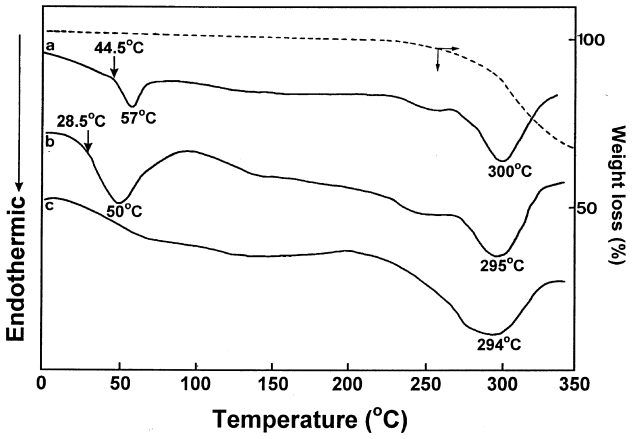

Fig. 4. DSC thermograms (solid lines) and TGA curves (dotted lines) of Eudragit E with different treatments: (a) original granule; (b) pulverized sample; (c) evaporated sample.

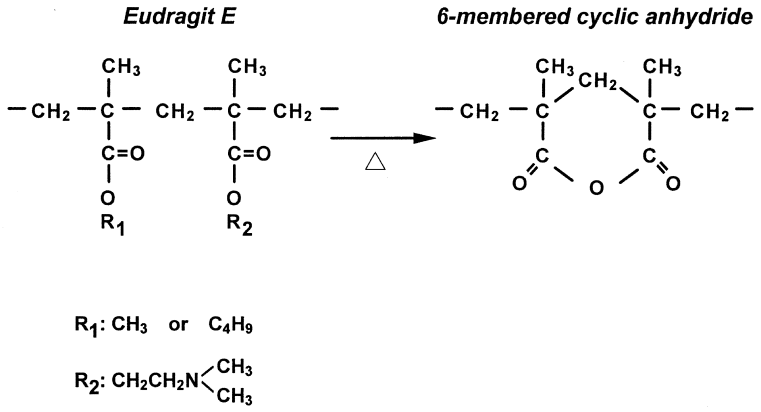

Fig. 5. Scheme for six-membered cyclic anhydride formation from Eudragit E by heating process.

cyclic anhydrides by heating the Eudragit E film. The peaks at 1801 and 1763 cm^{-1} seemed to be related to intermolecular and intramolecular condensation, respectively [19]. Since their peak intensity ratio of 1763 cm^{-1}/1801 cm^{-1} was about 2.5, the higher peak intensity at 1763 cm^{-1} implies the predominant role of the intramolecular condensation in the anhydride formation in Eudragit E film.

Other evidence of anhydride formation in the Eudragit E film during the heating process in the absence of catalyst or initiator is also found at the frequency of 1007 cm^{-1}, as shown in Figs 1–3. Obviously, the peak intensity at 1007 cm^{-1} increased above 180°C and reached a steady state at 280°C. This peak, due to the asymmetric stretching mode of C–O–C, strongly supports the cyclic anhydride formation from the ester condensation in the Eudragit E film. The peaks at 1273 and 1246 cm^{-1} assigned to the C–O stretching band of the ester group in Eudragit E shifted gradually to 1246 cm^{-1} with an increase of temperature. Furthermore, the peak at 1153 cm^{-1} corresponding to the C–N stretching absorption of aliphatic amines and/or C–O stretching vibration of ester groups obviously shifted to 1134 cm^{-1} with the increase of temperature. Since the peaks at 2820 and 2770 cm^{-1} due to the dimethylamino groups disappeared beyond 280°C, the peak at 1134 cm^{-1} might be attributable to the C–O band in the C–O–C stretching mode. This shift from higher frequency to lower frequency is consistent with the result of Galbiati et al. [20], in which the C=O stretching mode at 1700 cm^{-1} shifted upwards and the corresponding C–O mode shifted downwards. The unbalanced distribution of electron density induced by C=O might be responsible for this shifting phenomenon.

The DSC thermogram of Eudragit E polymer treated by different methods is shown in Fig. 4. Two endothermic peaks at 57 and 300°C were observed from the DSC curve of the Eudragit E granules (Fig. 4a). The onset temperature at 44.5°C for the first endothermic peak might be due to the glass transition temperature (T_g) of Eudragit E polymer, which was consistent with the T_g value of 45.3°C for the glassy methacrylic polymer of Eudragit E [21]. Once the Eudragit E granules were pulverized, however, the T_g value changed from 44.5 to 28.5°C (Fig. 4b). This might be because the pulverizing effect induced the structure of the Eudragit E polymer to turn into a more amorphous state, leading to the decrease of the glass transition temperature of the Eudragit E polymer. On the other hand, the T_g disappeared from the DSC curve for the evaporated sample in the same process as film preparation. The slower evaporation of organic solvent from the ethanolic Eudragit E solution induced the ordered recrystallization of polymer to form a crystalline methacrylic polymer rather than a glassy one. The TGA curve also exhibited 30% of weight loss between 180 and 350°C, which corresponds to almost complete loss of the dimethylamino group from Eudragit E, as shown in Figs 2 and 3. The IR spectral intensity at a steady level in the initial heating course (30–180°C) by the reflectance FTIR/DSC system also confirmed this result. The appearance of the endothermic peak at 300°C is unclear, but it might perhaps be attributed to the melting temperature of the mixture of the residual Eudragit E and/or anhydride sample. Further studies should be carried out.

Several investigations have reported that the carboxylic anhydrides can be prepared from carboxylate esters in the presence of metal catalysts and promoters [22–24]. In the present study, reflectance FTIR spectra showed the formation of six-membered cyclic anhydrides from the Eudragit E film only by heating. Thus, in the absence of catalyst or initiator, the scheme for the thermal-induced anhydride formation by ester condensation is shown in Fig. 5. Its detailed mechanism is still unknown, but the formation of a six-membered ring structure in the most stable state can be predicted. Perhaps the free radical induced by the higher temperature in the ambient condition may to be related to the reaction. Moreover, the higher electronegativity (unshared electron pair) of nitrogen in the dimethylamino group might also be taken into account for improving the ester condensation during the heating process. The anhydride formation started beyond 180°C. Once the temperature reached 280°C, the reaction sites were almost

exhausted and the condensation process was slowed down. In conclusion, six-membered cyclic anhydrides can easily form through heating Eudragit E polymer via the intramolecular ester condensation. The detailed mechanism of ester condensation in Eudragit E will be investigated in the future.

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