

Microscopic Fourier Transform Infrared/Differential Scanning Calorimetry System Used to Study the Different Thermal Behaviors of Polymethacrylate Copolymers of Eudragits RS, RL, E 30D, or E

SHAN-YANG LIN, HUI-LING YU

Biopharmaceutics Laboratory, Department of Medical Research and Education, Veterans General Hospital-Taipei, Taipei, Taiwan, Republic of China

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ABSTRACT: The thermal stability of Eudragits RL, RS, E 30D, and E films was qualitatively investigated by the reflectance Fourier transform infrared microspectroscopy equipped with differential scanning calorimetry (FTIR/DSC microscopic system). DSC and thermogravimetric analysis (TGA) were also used to study the thermal behavior of the granules of the raw material and the film of these polymers. The results indicate that the Eudragit RL, RS, or E 30D polymer exhibited a higher thermal-stable behavior, but Eudragit E easily formed the six-membered cyclic anhydride through heating process via the inter- or intramolecular ester condensation. The leaving group in Eudragit E molecule was larger than that in Eudragit E 30D, and the leaving group of salt in Eudragit RS or RL was too stable to polycondense. The DSC thermograms and TGA curve also confirmed this result. © 2000 John Wiley & Sons, Inc. *J Appl Polym Sci* 78: 829–835, 2000

Key words: Eudragit RS, RL, E 30D, E, thermal stability; anhydride formation; differential scanning calorimetry; thermogravimetric analysis; reflectance Fourier transform infrared/differential scanning calorimetry microspectroscopy

INTRODUCTION

Polymethacrylates are synthetic cationic or anionic polymers of dimethyl-aminoethylmethacrylates, methacrylic acid, and methacrylic acid esters in varying ratios.^{1,2} They are used in pharmaceutical formulations as film coating agents, bindings, direct-compression excipients, and gel bases.^{1,2} Under the trade name of Eudragits, several series have been included in the monograph of USP/NF (United States Pharmacopeia/National Formulary) with a nonproprietary name of methacrylic acid copolymer. Eudragits RS, RL,

and E 30D have been used as water-insoluble film coats for sustained-release products, Eudragits RS and RL referred to as ammonio-methacrylate copolymers in the USP/NF monograph, and are prepared by copolymerization of ethyl acrylate, methyl methacrylate, and trimethyl-ammonio-ethyl methacrylate chloride with mole ratio of 1:2:0.1 for Eudragits RS and 1:2:0.2 for Eudragit RL. Eudragit RL films are more permeable than Eudragit RS, due to the different content of quaternary ammonium groups. Eudragit E 30 D is an aqueous latex dispersion (30% solid content) of a neutral copolymer consisting of poly(ethyl acrylate and methyl methacrylate) (mole ratio: 2:1). Eudragit E is a cationic polymer prepared by copolymerization of butyl methacrylate, 2-dimethyl aminoethylmethacrylate, and methyl methacry-

Correspondence to: S.-Y. Lin (sylin@vghtpe.gov.tw).

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late with mole ratio of 1:2:1, and always used as a film-coating former. Eudragit E 30D is directly used after dilution. It is not only insoluble in water but also pH independent. However, Eudragit E must dissolve in organic solvent during usage but is soluble in gastric fluid below pH 5.0.

It has been suggested that the raw material of Eudragits should be stored at a temperature within 5–30°C to maintain their stability.² This reveals the role of temperature in the stability behavior of these polymers. Our previous studies on the thermal stability of Eudragits L, S, L 30D, or acrylic acid polymer of carbopol using microscopic Fourier transform infrared spectroscopy equipped with differential scanning calorimetry (FTIR/DSC system) have found the formation of a six-membered cyclic anhydride within the molecular structures via inter- or intrapolymer condensation in heating process.³ The microscopic FTIR/DSC system has been applied to simultaneously investigate the correlation between the thermal treatment and the structural changes of drugs, fish oil, liquid crystal, skins, and polymers using a transmission method.^{4–10} Moreover, reflectance FTIR/DSC microspectroscopy also has been applied to determine the anhydride formation in Eudragit L and E films, and the thermal stability of α -crystallin.^{11–15} This system offers a fast, simple, precise, and reproducible operation to determine the thermal-dependent characteristics of samples. The purpose of this study was to systematically investigate the thermal behavior of the film form of Eudragits RS, RL, E 30D, or E by reflectance FTIR/DSC microspectroscopic technique. DSC and thermogravimetric analysis (TGA) were also used to study the thermal behavior of the granules of the raw material and the film of these polymers.

EXPERIMENTAL

Materials

Eudragits RS-100 and RL-100 (white-opaque granules, molecular weight: 150,000), E 30D (aqueous latex dispersion, molecular weight: 800,000), as well as E-100 (light-yellow granules, molecular weight: 150,000) were kindly provided by Rohm Pharma (Darmstadt, Germany). Aluminum foil was purchased from Reynolds Metals Co. (Virginia, USA). Anhydrous ethanol was of a reagent grade, obtained from Nakalai Tesque (Kyoto, Japan). The structural

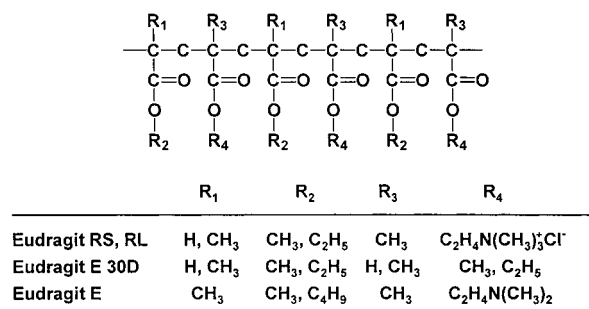


Figure 1 Structural formula of Eudragits RS, RL, E 30D, and E.

formula of Eudragits RS, RL, E 30D, and E is shown in Figure 1.

Preparation of Eudragits RS, RL, E 30D, and E Films Coated on Aluminum Foil

A dilute Eudragits RS, RL, E 30D, and E solution (6% in anhydrous ethanol), or an Eudragit E 30D dispersion (diluted with water), was dropped respectively on aluminum foil. A spin coater (SC-300, E. H. C. Co., Taiwan, ROC) was used to prepare the uniform and smooth film of each sample, which was then vacuum-dried at 30°C for 12 h. The thickness of each film coated on foil was about 8–10 μm .

Reflectance FTIR/DSC Microspectroscopic Study

The film of each sample coated on aluminum foil was carefully cut to measure 6 \times 6 mm. This sample piece was directly inserted into a DSC microscopy cell (FP 84, Mettler, Switzerland). The DSC microscopy cell was then placed on the stage of the microscope equipped 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.^{11–15}

Thermal Analysis of Eudragits RS, RL, E 30D, and E1 Samples

A certain amount of the ethanolic Eudragits solution, or Eudragit E 30D aqueous dispersion was placed 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 30°C and examined by differential scanning calorimetry (DSC-910, TA Instru. Inc., USA) at a heating rate of 5°C/min with an open pan system in a stream of N₂ gas. The DSC cell

was calibrated with indium. The granules of Eudragits RS, RL, or E were respectively and directly examined as control. Thermogravimetric analysis (TGA-951, Du Pont, USA) was also performed at the same heating rate.

RESULTS AND DISCUSSION

Three-dimensional plots of the thermal-dependent reflectance FTIR spectra of the Eudragits RS, RL, E 30D, and E films between 3100 and 2800 cm^{-1} , and 1900 and 900 cm^{-1} , are shown in Figure 2. The peaks in the range between 3100 and 2800 cm^{-1} relate to the C—H stretching bands, the peak in the range between 1800 and 1650 cm^{-1} is due to the C=O stretching vibrational groups, and the peak in the range between 1350 and 900 cm^{-1} corresponds to the C—O stretching vibration mode.¹⁶ Figures 2(A) and 2(B) indicate no change of the frequency and peak intensity of the IR spectra for Eudragit RS and RL films with the increase in temperature. The peaks within 2950–3000 cm^{-1} assigned to the stretching vibrations of CH_2 and CH_3 , the peak at 1763 cm^{-1} corresponds to the C=O ester vibration, and the peak at 1153 cm^{-1} is due to the C—O ester vibration, respectively. Several peaks specified in Figures 3(A) and 3(B) also kept a constant intensity in heating process. Our previous study³ has evidenced that Eudragits S and L could induce anhydride formation via inter- or intrapolymer polycondensation, in which the cyclic anhydride-related IR peaks might appear near 1801, 1759, and 1006 cm^{-1} , respectively. In the present study, however, the absence of cyclic anhydride-related IR peaks in the IR spectra of Eudragit RS and RL suggested no anhydride formation in Eudragit RS and RL by heating treatment. This also indicates a higher thermal stability of the film of Eudragit RS or RL. A lot of free carboxylic acids might be responsible for the easier anhydride formation in the structural formula of Eudragits S and L than in Eudragits RS and RL, which lack free carboxylic acids.¹⁷ Eudragit E 30D also exhibited the same thermal behavior as the Eudragits RS and RL [Figures 2(C) and 3(C)]. Although a transitional temperature was slightly found at 180°C for the 2982 and 2955 cm^{-1} peaks of Eudragit E 30D, there was no additional anhydride-related IR peaks near 1801, 1759, and 1006 cm^{-1} . This also reveals the higher thermal stability of Eudragit E 30D film.

Cyclic polycondensation was performed in the Eudragit E film via heating process, as shown in Figures 2(D) and 3(D). The increase of temperature gradually decreased the intensity of some peaks, and some peaks appeared at the specified temperature. By heating the Eudragit E film from 30 to 180°C, the intensity of the peaks within 3100–2600 cm^{-1} slowly reduced, in which the peaks at 2955 and 2874 cm^{-1} were assigned to asymmetric and symmetric CH_3 groups of Eudragit E, and the peaks at 2820 and 2770 cm^{-1} were due to the dimethylamino groups of Eudragit E. Moreover, the peak at 1732 cm^{-1} assigned to the ester carbonyl group also exhibited the same behavior. Once the Eudragit E film was heated beyond 180°C, the intensity of the peaks at 2820 and 2770 cm^{-1} and the peak at 1732 cm^{-1} for Eudragit E film began to decrease markedly with the increase of temperature [Figures 2(D) and 3(D)]. When the temperature reached 280°C, both peaks at 2820 and 2770 cm^{-1} apparently flattened out, suggesting the complete loss of dimethylaminoethyl group. Another three new additional bands at 1801, 1763, and 1006 cm^{-1} appeared from near 180°C, however, and their peak intensities kept increasing with temperature [Figures 2(D) and 3(D)]. The new peaks at 1801 and 1763 cm^{-1} were assigned to the asymmetric and symmetric stretching vibration of carbonyl group in anhydride, implying the formation of anhydride in Eudragit E film by inter- and/or intramolecular condensation within the Eudragit molecules during heating process.^{18–20} Pretsch et al. have pointed out the carbonyl stretching vibration of six-membered cyclic anhydrides at 1800 and 1760 cm^{-1} ,^{18,19} rather than at 1850 and 1775 cm^{-1} for five-membered cyclic anhydrides, indicative of the formation of six-membered cyclic anhydride. The peaks at 1801 and 1763 cm^{-1} are related to intermolecular and intramolecular condensation, respectively,²⁰ whose peak intensity ratio of 1763/1801 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. The intensity of another new peak at 1006 cm^{-1} increased above 180°C and reached to steady state at 280°C. This peak due to the asymmetric stretching mode of C—O—C strongly confirms the cyclic anhydride formation from the ester condensation of Eudragit E film [Figures 2(D) and 3(D)]. The cyclic anhydride formed more easily Eudragit E film than in Eudragit RS, RL, or E 30D film due to the different substituent in Eudragit E film

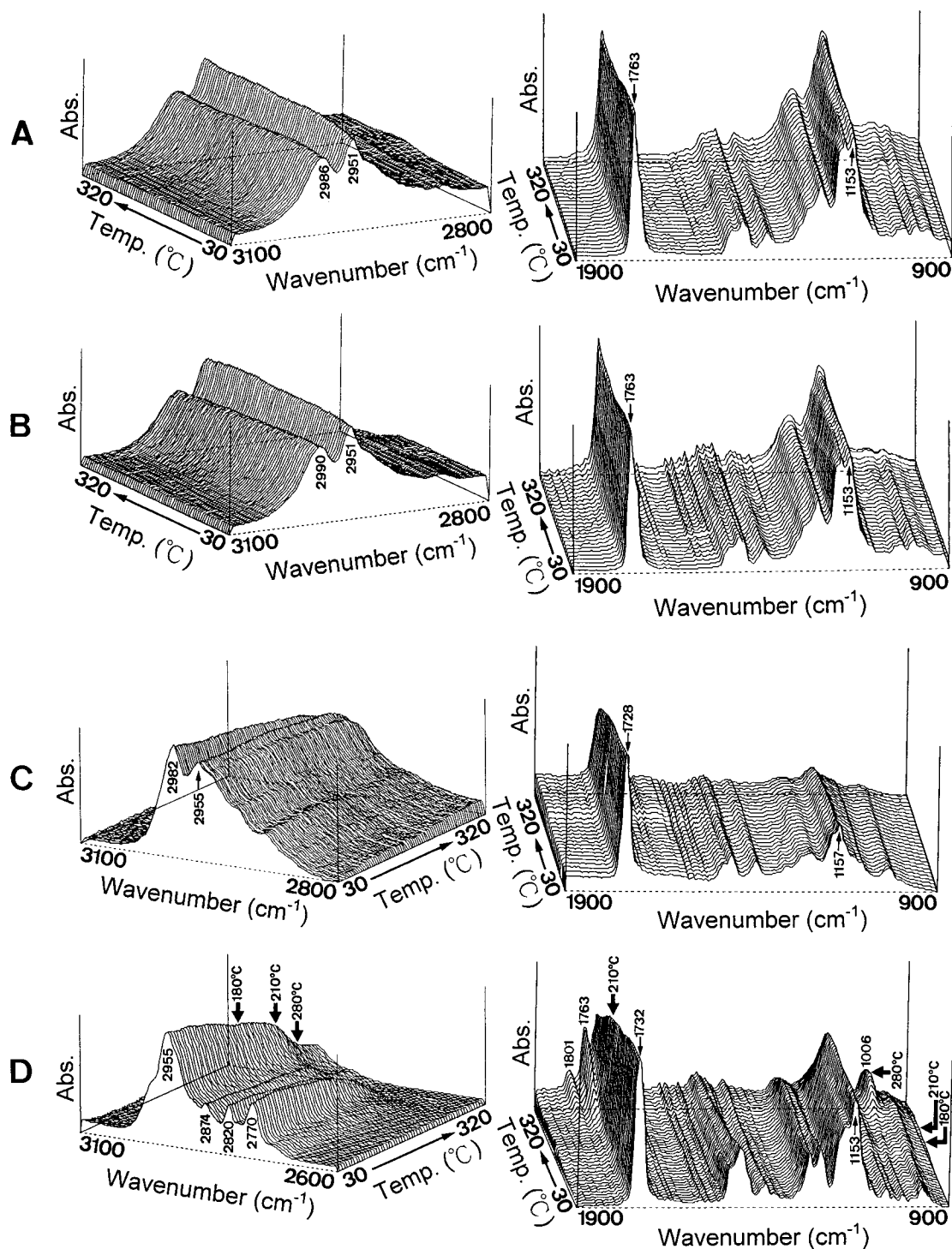


Figure 2 Three-dimensional plots of reflectance FTIR spectra of Eudragits RS, RL, E 30D, and E films with respect to temperature. (A) Eudragit RS, (B) Eudragit RL, (C) Eudragit E 30D, and (D) Eudragit E.

than in Eudragit E 30D. Furthermore, the partial substituent in Eudragit RS or RL film was salt, which was too stable to polycondense.

DSC thermograms and TGA curves of the Eudragits RS, RL, E 30D, and E polymers are plotted in Figure 4. Obviously, the shape of DSC

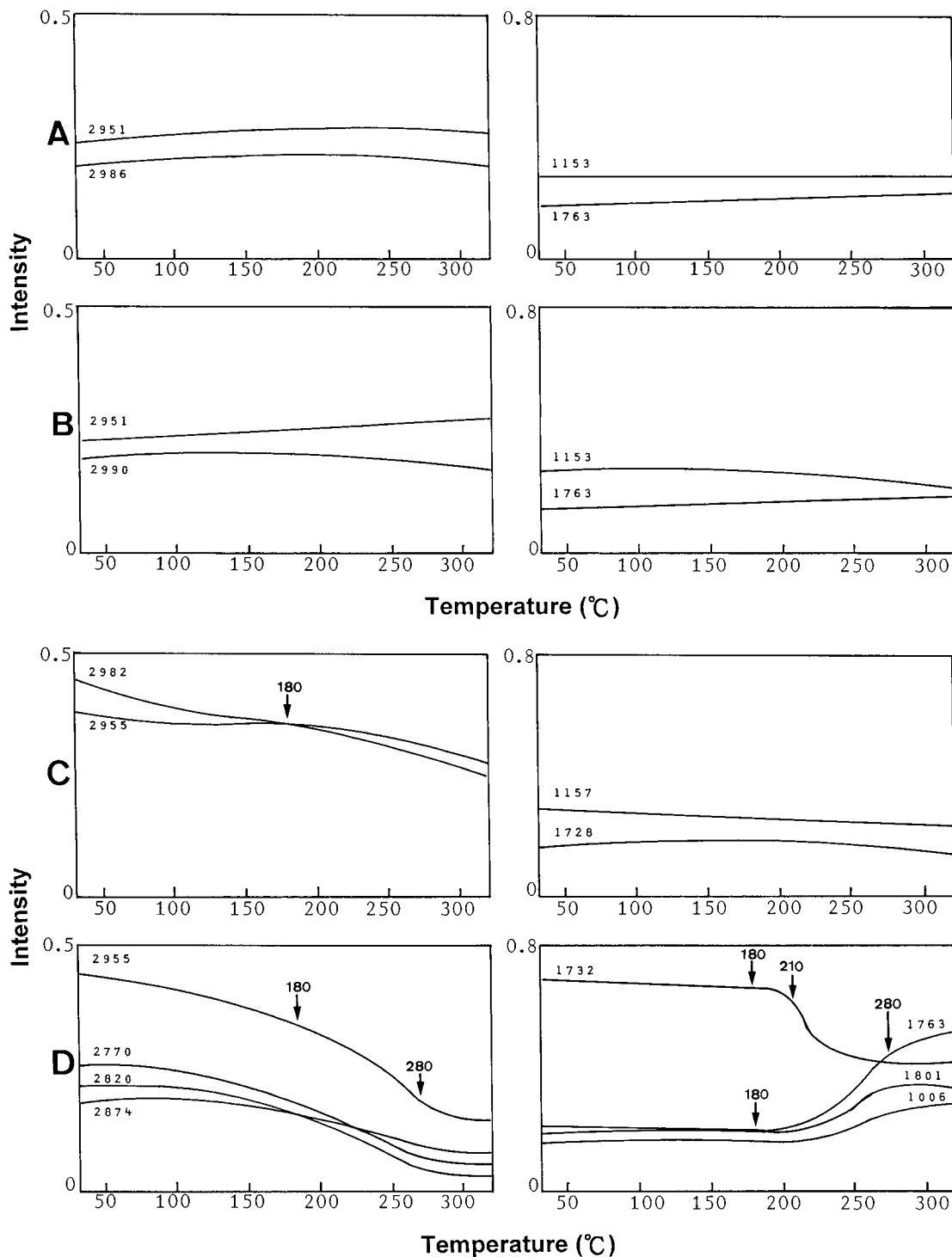


Figure 3 Temperature dependencies of the FTIR peak intensity for the various IR bands of Eudragits RS, RL, E 30D, and E film. (A) Eudragit RS, (B) Eudragit RL, (C) Eudragit E 30D, and (D) Eudragit E.

thermograms for Eudragits RL and RS was similar to each other except the difference in peak position. The endothermic peaks at 62°C for the

granular sample of both Eudragits RL and RS was due to the evaporation of unbound water adsorbed and/or its glass transition temperature

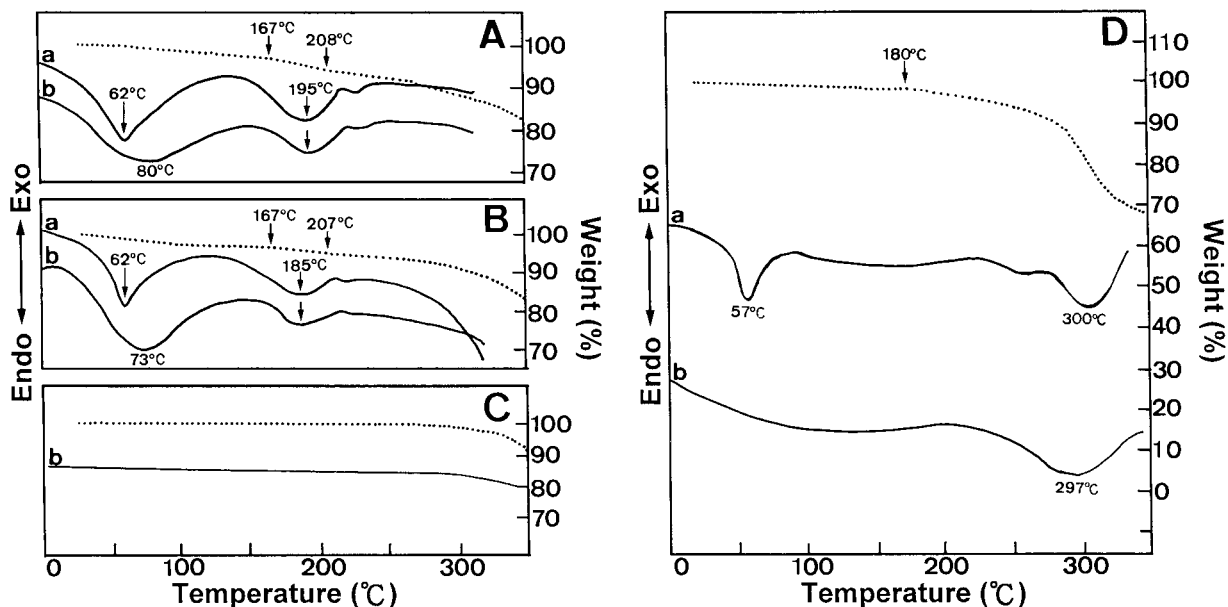


Figure 4 DSC thermograms (solid line) and TGA curves (dotted line) of Eudragits RS, RL, E 30D, and E polymers. (A) Eudragit RS, (B) Eudragit RL, (C) Eudragit E 30D, and (D) EudragitE. (a) granule; (b) film.

(T_g). This endothermic peak for the granules of Eudragit RL or RS was found to shift from 62 to 80 or 73°C for the film form of Eudragit RL or RS, respectively [Figures 4(A) and 4(B)]. This phenomenon is attributable mainly to the ordered structure in film form after solvent evaporation. The endothermic peak at 195 or at 185°C might be attributed to the fusion of melting point for Eudragit RL or RS, respectively. Before melting point, only slightly weight loss in TGA curves for both Eudragits due to the unbound water. On the other hand, there was no change in DSC thermogram for Eudragit E 30D up to near 300, suggesting a higher thermal property of Eudragits E 30D than that Eudragit RS or RL.

On the other hand, the DSC thermogram and TGA curve of Eudragit E polymer are illustrated in Figure 4(D). Two endothermic peaks at 57 and 300°C were observed from the DSC curve of the Eudragit E granules [Figures 4(D-a)]. The endothermic peak at 57°C for the granular sample of Eudragit E was due to the glass transition temperature.¹⁴ The first endothermic peak disappeared from the DSC curve for the evaporated Eudragit E film, but was instead a broad curve. This was different from that in the DSC thermogram of Eudragit RL or RS film [Figures 4(A) and 4(B)], as monomers in each Eudragit polymer might be different. The slower evaporation of organic solvent from the ethanolic Eudragit E solu-

tion induced the ordered crystallization of the polymer to form crystalline methacrylic polymer rather than glassy one. TGA curve also exhibited 31.4% weight loss between 180 and 350°C, which corresponds to the complete loss of dimethylamino group of Eudragit E and the formation of anhydride, as shown in Figures 2 and 3. The constant IR spectral intensity in the range of 30–180°C by reflectance FTIR/DSC system also confirmed this result. The endothermic peaks at 300 or 297°C might be mainly attributable to the loss of water by condensation that resulted in the anhydride formation of the Eudragit E sample.¹⁴ Several studies have reported that the carboxylic anhydrides can be prepared from carboxylate esters in the presence of metal catalysts and promoters.^{21–23} In the present study, reflectance FTIR spectra evidenced the formation of six-membered cyclic anhydrides from the Eudragit E film by heating only. The larger leaving group with higher electronegativity of nitrogen in the dimethylamino group within Eudragit E polymer than in Eudragit RS, RL, or E 30D might also be taken into account to improve the ester condensation in 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 slower down.

In conclusion, Eudragits RL, RS, or E 30D polymer exhibited a higher thermal-stable behavior, but the six-membered cyclic anhydrides formed easily through heating the Eudragit E polymer via the inter- or intramolecular ester condensation.

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