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Temperature-dependent anhydride formation of Eudragit L-100 films determined by reflectance *FT*i.r./d.s.c. microspectroscopy

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A novel reflectance Fourier transform infra-red/differential scanning calorimetry (*FT*i.r./d.s.c.) microscopic system was used to determine the temperature-dependent anhydride formation of Eudragit L-100 film. A three-dimensional plot of the reflectance *FT*i.r. spectra of Eudragit L film with respect to temperature was obtained. With the increase of heating temperature, three bands at 1804, 1763 and 1006 cm^{-1} suddenly appeared beyond 206°C and these peak intensities became markedly stronger. The appearance of these peaks during heating might be attributed to the anhydride formation by inter- or intrapolymer condensation, since acid anhydrides give two carbonyl stretching vibrations at 1800–1750 cm^{-1} and one antisymmetric C—O—C stretching band.

(Keywords: films; anhydride formation; reflectance microspectroscopy)

Introduction

Eudragit L-100 is a copolymer of methacrylic acid and methyl methacrylate with 1 : 1 molar ratio prepared by emulsion polymerization. It is used as an enteric-coating polymer in the pharmaceutical industry because it contains carboxylic groups which can transform to carboxylate groups in the pH range 5–7 by salt formation with alkali or amines[1,2]. Since the Eudragit L-100 polymer contains many carboxylic groups on the polymer chain, it may be predicted to form cyclic anhydrides within and/or between polymer chains during heating, since certain dicarboxylic acids in organic compounds certainly yield anhydrides on simple heating[3].

Lin and co-workers have recently used the newly developed technique of microscopic Fourier transform infra-red (*FT*i.r.) spectroscopy combined with differential scanning calorimetry (d.s.c.) to simultaneously investigate the effect of thermal treatments on the i.r. spectra and structural changes of samples such as polymorphs or solvates of drugs[4,5], the thermal stability of encapsulated oil[6], thermotropic lipid transition of skin[7], the curing kinetics of silicon elastomer[8], and drug–polymer interactions and the glass transition of polymers[9,10]. This novel *FT*i.r./d.s.c. microscopic system uses a transmission method and is a simple, quick and powerful tool for determining the temperature-dependent characteristics of samples. The sample is sealed within a KBr disc and placed on the d.s.c. microscopy cell, and then directly determined by transmission *FT*i.r. microspectroscopy.

Recently, research has been reported on the use of reflectance *FT*i.r. spectroscopy to study the insoluble monolayers at the air/water interface, adhesive films on aluminium, and fossil algae on organic-rich shales[11–13]. However, very little is known about the use of reflectance *FT*i.r./d.s.c. microspectroscopy to investigate the temperature-related structural change of samples. The purpose of this study is to develop a reflectance *FT*i.r./d.s.c. microspectroscopic technique for determining temperature-dependent anhydride formation in Eudragit L-100 film, instead of using conventional transmission *FT*i.r. microscopic spectroscopy combined with a thermal analyser.

Experimental

Materials. Eudragit L-100 polymer was kindly donated by Rohm Pharma (Darmstadt, Germany). Aluminium foil was purchased from Reynolds Metals Co. (Virginia, USA). Anhydrous ethyl alcohol was reagent grade, obtained from Nakalai Tesque (Kyoto, Japan).

Preparation of Eudragit L films on aluminium foil. A dilute Eudragit L-100 solution (6% in anhydrous ethyl alcohol) was dropped on the aluminium foil. A spin coater (SC-300, E.H.C. Co., Taiwan, ROC) was used to prepare the Eudragit L film. The thickness of Eudragit L film coating on the foil was 8 μm, measured by a thickness tester (α-step 200, Tencor Instrument Co.) with an accuracy of 100 nm.

Thermal analysis of Eudragit L films. A sample of the ethanolic Eudragit L-100 solution was cast onto the

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glass plate and then evaporated at room temperature. The film was taken off and vacuum dried for 24 h at 60°C, and stored in a sealed container until used. The film was examined by d.s.c. (DSC-910, TA Instruments Inc., USA) at a heating rate of 10°C min^{-1} with a closed pan system in a stream of N_2 gas. Thermogravimetric analysis (t.g.a.) (TGA-951, Du Pont, USA) was also performed at the same heating rate.

Reflectance FT*i.r./d.s.c. microspectroscopic study.* The sample of Eudragit L film coated on aluminium foil was carefully cut to a size of 3 mm × 3 mm. This sample was directly inserted into the d.s.c. microscopy cell (FP 84, Mettler, Switzerland). The d.s.c. microscopy cell was then placed on the stage of the microscope equipped in the *FT*i.r. microscopic spectrometer (Micro FTIR-200, Jasco, Japan) with a MCT (mercury–cadmium telluride) detector. The system was operated in the reflectance mode. The position and focus of the sample were adjusted by the microscope. The i.r. beam was imaged onto the sample with a 16× Cassegrainian objective. The desired sample size (300 μm × 300 μm) for determination was selected and defined by means of an Aperture Through Optical System (ATOS) for analysis. The temperature of the d.s.c. microscopy cell was monitored with a central processor (FT80HT, Mettler, Switzerland). The heating rate of the d.s.c. assembly was controlled at 5°C min^{-1}. This reflectance *FT*i.r./d.s.c. system was operated by a non-isothermal method. The non-isothermal method used a heating measurement programme to heat the sample from 30 to 320°C, and the d.s.c. thermograms and i.r. spectra could be simultaneously recorded. The reflectance i.r. spectra were collected at an angle of incidence centred at 30° taken with a resolution of 4 cm^{-1} and 100 scans.

Results and discussion

Figure 1 shows the three-dimensional plots of the reflectance *FT*i.r. spectra of Eudragit L film between 1630 and 1870 cm^{-1}, and between 900 and 1350 cm^{-1}, as a function of temperature. Apparently, the frequency and peak intensity of the i.r. spectra changed with the increase of temperature. The peaks between 1750 and 1660 cm^{-1}, assigned to the carboxylic ester and acid of Eudragit L, were slightly modified below 206°C, but beyond this temperature, two specific bands at 1804 and 1763 cm^{-1} suddenly appeared and their peak intensities became stronger with increasing temperature. The appearance of these peaks during the heating process might be attributed to the anhydride formation by inter- or intrapolymer condensation, since acid anhydrides give two carbonyl stretching absorptions near 1800 and 1750 cm^{-1} (ref. 14). Pretsch *et al.*[15] have pointed out that the carbonyl stretching vibration of six-membered ring cyclic anhydrides is near 1800 and 1760 cm^{-1}, rather than near 1850 and 1775 cm^{-1} for five-membered ring cyclic anhydrides. This suggests that six-membered ring cyclic anhydride is formed by heating the Eudragit L film. The peak at 1006 cm^{-1} due to the antisymmetric stretching mode of C–O–C was also found beyond 206°C, which might act as confirmatory evidence of the cyclic anhydride formation on Eudragit L polymer. This also implies that the anhydride formation was temperature-dependent. The t.g.a. curve and d.s.c. thermogram of Eudragit L film also support this result, as shown in *Figure 2.* An endothermic peak between 200 and 230°C was found in the d.s.c. thermogram. This endothermic peak might be attributed to the loss of water by condensation, resulting in the anhydride formation of Eudragit L film. The t.g.a. curve exhibited 4.8% weight loss between 200 and 225°C: 4.8% of this weight loss is equal to a water loss of 4.82% from Eudragit L (molecular weight 13 500, with 726 molecules of methacrylic acid and 362 molecules of water produced) by calculation. Moreover, the condensation reaction of the polymer under normal conditions caused loss of water vapour and produced an endothermic peak which

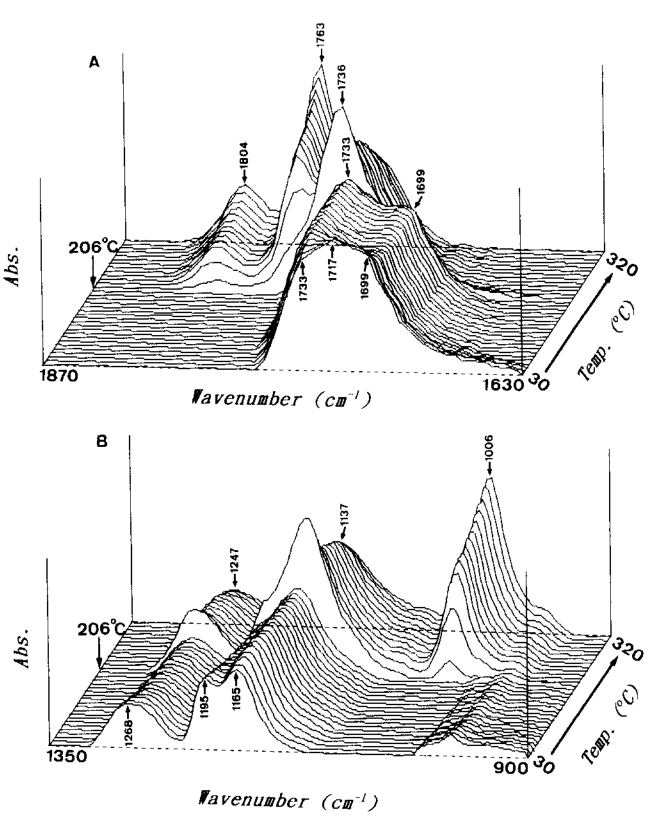

Figure 1 Three-dimensional plots of reflectance i.r. spectra of Eudragit L film with respect to temperature

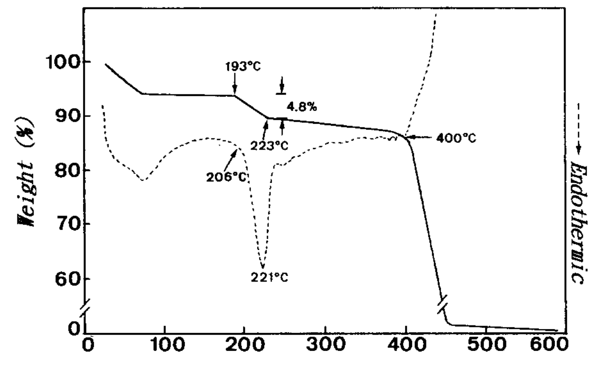

Figure 2 T.g.a. curve (——) and d.s.c. thermogram (– – –) of Eudragit L film

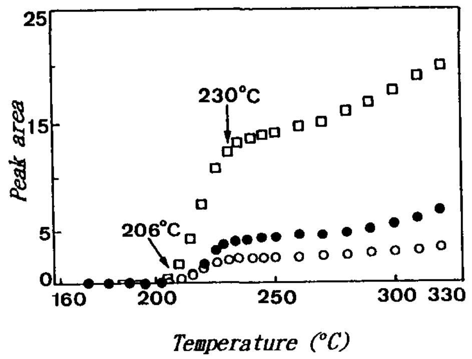

Figure 3 Kinetics of the temperature-dependent anhydride formation in Eudragit L polymer: ○, 1804 cm^{-1}; ●, 1763 cm^{-1}; □, 1006 cm^{-1}

was large enough to obliterate the exothermic peak due to crosslinking[16].

The change in peak intensity of three specified peaks (1804, 1763 and 1006 cm^{-1}) assigned to the stretching vibration of C=O and to the antisymmetric stretching mode of C–O–C in Eudragit L with temperature is also clearly revealed in *Figure 1*. With the increase of temperature, the peak intensities of the three specified peaks increased markedly. The kinetics of anhydride formation is plotted in *Figure 3*. The anhydride formation is obviously a two-stage process after heating beyond 206°C. In the initial stage (206–230°C), the anhydride production was rapid, but the second stage was slower. This might be because the inter- and/or intramolecular condensation within the Eudragit L polymer took place easily during the initial stage, since many reaction sites existed. However, beyond this stage the reaction sites were almost exhausted, and the condensation process could not take place so easily.

The results reported here show that reflectance *FT*i.r./d.s.c. microspectroscopy is a valuable tool for the easy investigation of anhydride formation in Eudragit L polymer. The non-isothermal or isothermal kinetics and activation energy of anhydride formation of Eudragit L-100 will be evaluated in the future.

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