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

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A reflectance Fourier transform infra-red (*FT* i.r.)/differential scanning calorimetry (d.s.c.) microscopic system was used to investigate the reaction rate and reaction order of anhydride formation in Eudragit L-100 film by isothermal stability study. The accelerated stability testing was performed at 160, 180, 190 and 200°C for 3 h. The changes in three-dimensional reflectance *FT* i.r. spectra of Eudragit L film with respect to heating time were obtained. The results indicate that the peak areas of three specific i.r. peaks at 1804, 1763 and 1006 cm^{-1}, assigned to the carbonyl stretching vibration and the asymmetric stretching of C–O–C in Eudragit L-100 film, gradually enlarged with increasing time. The enlargement of these peak areas during the heating process might be attributed to the anhydride formation by inter- or intrapolymer condensation. The order of this isothermal kinetics for anhydride formation in Eudragit L-100 film was 1.85, which might be considered as a second-order reaction, and the activation energy was 51.25 kcal mol^{-1}.

(Keywords: anhydride formation; reflectance microspectroscopy; isothermal kinetics)

INTRODUCTION

To ensure the shelf-life of drugs and polymers, accelerated stability testing under exaggerated conditions has been performed to accelerate the degradation process and then used to predict the product stability[1-3]. Accelerated stability testing is largely based on an empirical relationship of temperature to an observed chemical reaction-rate constant. Information about the room-temperature stability is then extrapolated from these accelerated data by using the Arrhenius law, where the logarithm of the rate constant of the process is related to the inverse of the absolute temperature[1-3]. The test is generally performed under isothermic conditions, that is with parallel storage of samples at differing, but in each case constant, temperatures.

A newly developed Fourier transform infra-red (*FT* i.r.) microspectroscope combined with differential scanning calorimetry (d.s.c.) has been used to simultaneously study the effect of thermal treatments on the i.r. spectra and structural changes of samples such as polymorphs or solvates of drugs[4,5], thermal stability of encapsulated oil[6], thermotropic transition of skin lipid and protein[7], curing kinetic of silicon elastomer[8], and drug–polymer interaction and glass transitions of polymer[9,10]. This novel *FT* i.r./d.s.c. microscopic system using the transmission method is a simple, quick and powerful tool for determining the heat-dependent characterization of samples.

Recently, some researchers have reported the use of reflectance *FT* i.r. spectroscopy to study the insoluble monolayers at an air–water interface, adhesive films on aluminium, and fossil algae on organic-rich shales[11-13]. Lin *et al.* have successfully used reflectance *FT* i.r./d.s.c. microspectroscopy to investigate the polycondensation of Eudragit E-100 film cast on aluminium foil by a non-isothermal method, which is easier than transmission *FT* i.r./d.s.c. microspectroscopy[14,15]. The cast sample was placed in the d.s.c. microscopy cell and then directly studied by reflectance *FT* i.r. microspectroscopy under thermal treatment. The purpose of this study is to investigate the heat-dependent anhydride formation of Eudragit L-100 film under isothermal conditions by time-scan measurement using reflectance *FT* i.r./d.s.c. microspectroscopy. The activation energy of anhydride formation in Eudragit L-100 film was determined.

EXPERIMENTAL

Materials

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

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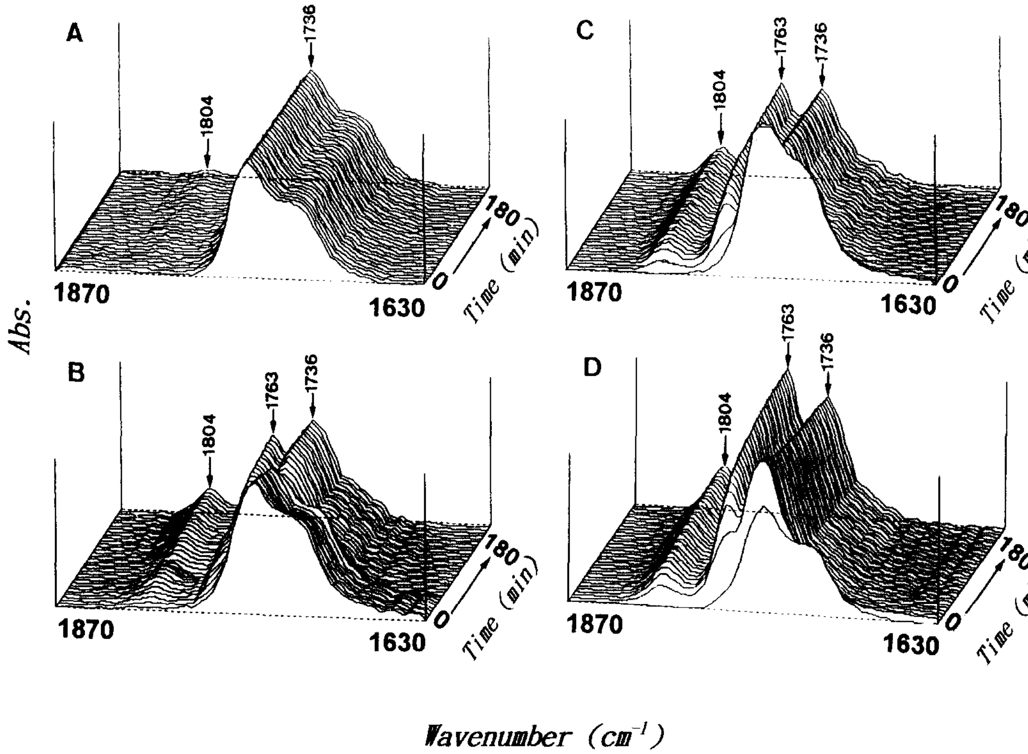

Figure 1 Three-dimensional plots of reflectance i.r. spectra of Eudragit L-100 films between 1870 and 1630 cm^{-1} with respect to the heating time Heating temperature: A, 160°C; B, 180°C; C, 190°C; D, 200°C

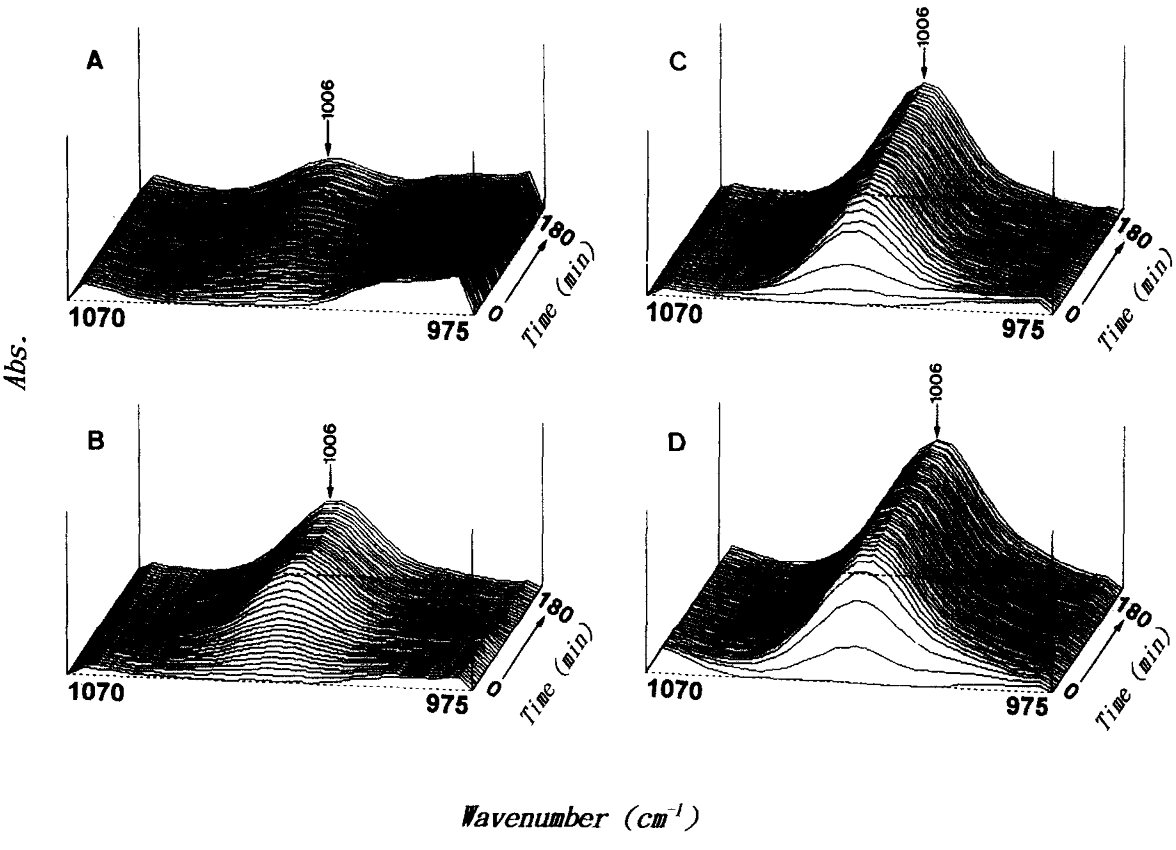

Figure 2 Three-dimensional plots of reflectance i.e. spectra of Eudragit L-100 film between 1070 and 975 cm^{-1} with respect to the heating time. Heating temperature: A, 160°C; B, 180°C; C, 190°C; D, 200°C

Preparation of Eudragit L films cast on aluminium foil

Six per cent concentration of Eudragit L-100 solution in anhydrous ethyl alcohol was dropped onto the aluminium foil. A spin coater (SC-300, E.H.C. Co., Taiwan, ROC) was used to prepare the Eudragit L film[14,15]. The thickness of Eudragit L film coated on the foil was 8 μm.

Reflectance FT*i.r./d.s.c. time-scan measurements*

The sample of Eudragit L film cased on aluminium foil was carefully cut to 3 mm × 3 mm in size. This sample disc was put directly 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 *FT*i.r. microscopic spectrometer (Micro FTIR-200, Jasco, Japan) which used an MCT detector. The system was operated in the reflectance mode. The position and focus of the sample were adjusted in 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}. I.r. reflectance was performed under isothermal conditions. The isothermal procedure used a time-scan measurement programme to control the d.s.c. microscopy cell at 160, 180, 190 or 200°C, maintaining the sample at each temperature for 180 min. The i.r. spectra and time were simultaneously recorded. The reflectance i.r. spectra were collected at an angle of incidence centred at 30° and taken with a resolution of 4 cm^{-1} and coadded 100 scans.

RESULTS AND DISCUSSION

Eudragit L-100 is a copolymer of methacrylic acid and methyl methacrylate with 1 : 1 molar ratio prepared by emulsion polymerization[16,17]. Since the Eudragit L-100 polymer contains many carboxylic groups on the polymer chains, it may form cyclic anhydrides within and/or between the polymer chains during the heating process, since certain dicarboxylic acids in organic compounds certainly yield anhydrides on simple heating[18].

Evidence of anhydride formation in Eudragit L-100 film during the heating process

Figures 1 and *2* show the three-dimensional plots of the reflectance *FT*i.r. spectra of Eudragit L-100 film between 1870 and 1630 cm^{-1}, and between 1070 and 975 cm^{-1}, respectively, as a function of temperature. Temperature-dependent changes in frequency and peak intensity of i.r. spectra of Eudragit L-100 film were found. Apparently, three specific peak intensities at 1804, 1762 and 1006 cm^{-1} gradually increased with increasing heating time at four temperatures. The higher the temperature used the stronger the peak intensity obtained. Two specific bands at 1804 and 1763 cm^{-1} gradually appeared with increasing heating time and their peak intensities became stronger. The appearance of these peaks during the heating process might be attributed to anhydride formation by inter- or intra-polymer condensation, since acid anhydrides give two carbonyl stretching absorptions, near 1800 and 1750 cm^{-1} (ref. 19). Pretsch *et al.*[20] have pointed out that the carbonyl stretching vibrations of six-membered-ring cyclic anhydrides are 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. Another specific peak at 1006 cm^{-1}, due to the antisymmetric stretching mode of C–O–C, was also found with the increased heating time, which might act as confirmatory evidence of cyclic anhydride formation on Eudragit L polymer. However, it also found that the peak intensity at 1736 cm^{-1} initially decreased with the increased heating time and then remained constant. The slight change in peak intensity at 1736 cm^{-1} during the heating process might be attributed to condensation between carboxylic acids in Eudragit L-100[14,15]. The carboxylic ester in Eudragit L-100 did not participate in the formation of anhydride, resulting in the constant peak intensity.

Kinetics study of anhydride formation in Eudragit L-100 film

The change in peak area of these three specific peaks (1804, 1763 and 1006 cm^{-1}), assigned to the stretching vibration of C=O and antisymmetric stretching mode of C–O–C in Eudragit L-100 with heating time, is also clearly revealed in *Figure 3*. Obviously, the peak area of each specific peak increased with the heating time and at constant heating temperature. The change in area for the peak at 1006 cm^{-1} was more pronounced. If we assume that the peak area at 200°C for 180 min has reached a constant plateau, the fractional conversion, α, can be expressed by[21] :

$$\alpha = A_{(t,T)}/A_0 \tag{1}$$

where $A_{(t,T)}$ is the peak area of the i.r. spectrum at time t and temperature T, and A_0 is the i.r. spectral peak area at 200°C for 180 min. The conversion curves for the three specific peaks at each temperature almost overlap, suggesting that the conversion rate given by each peak is the same. So the change in peak area at 1006 cm^{-1} was used as a model to determine the kinetics of anhydride formation of Eudragit L-100 during heating. The plot of fractional conversion as a function of time at different temperatures is shown in *Figure 4*. It is apparent that the rank order of anhydride formation is 200°C > 190°C > 180°C ≫ 160°C. This implies that the anhydride formation in Eudragit L-100 was heat-dependent.

The determination of the kinetic parameters is based on the general nth order rate expression as follows:

$$\mathrm{d}\alpha/\mathrm{d}t = k_{(\mathrm{T})}(1-\alpha)^n \tag{2}$$

where α is the fractional conversion obtained from equation (1), $k_{(\mathrm{T})}$ is the reaction rate constant at temperature T, and n is the reaction order. If equation (2) is integrated, equations (3) and (4) are obtained:

$$\text{if } n = 1 \qquad \ln(1-\alpha) = -k_{(\mathrm{T})}t \tag{3}$$

$$\text{if } n \neq 1 \qquad (1-\alpha)^{1-n} - 1/(n-1) = k_{(\mathrm{T})}t \tag{4}$$

By inputting the data from the fractional conversion–time plot at 200°C (*Figure 4*) a personal computer with curve-fitting program can be used to vary the n value in

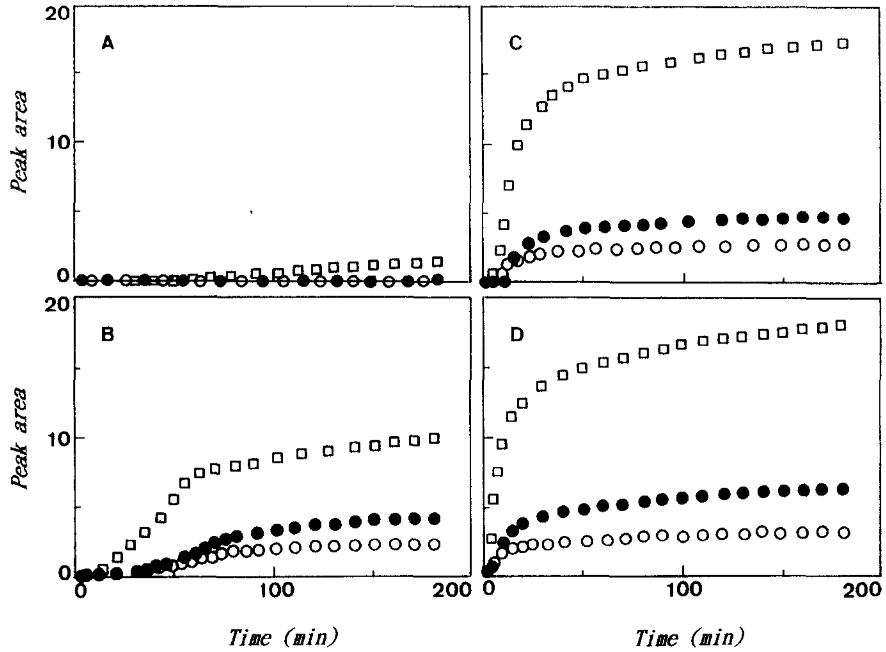

Figure 3 Kinetics of the temperature-dependent anhydride formation in Eudragit L-100 film. Heating temperature: A, 160°C; B, 180°C; C, 190°C; D, 200°C. □, 1804 cm^{-1}; ●, 1763 cm^{-1}; □, 1006 cm^{-1}

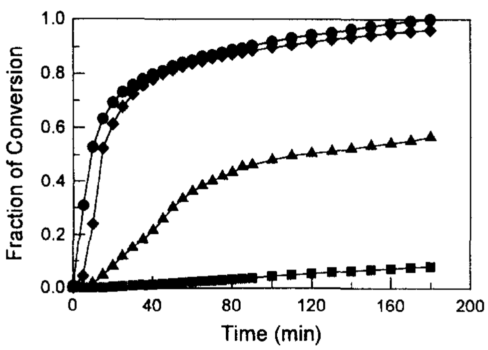

Figure 4 Conversion curves for Eudragit L-100 film as a function of heating time. ■, 160°C; ▲, 180°C; ◆, 190°C; ●, 200°C

Table 1 Selection of the reaction order from equations (3) and (4) using a curve-fitting program

Reaction order (n)	Correlation coefficient	$k_{(T)}$ (min^{-1})
0.00	0.85087	0.00048
1.00	0.96684	0.01966
1.50	0.99245	0.04292
1.60	0.99483	0.05046
1.70	0.99640	0.05944
1.80	0.99718	0.07013
1.85	0.99729	0.07622
1.90	0.99722	0.08288
2.00	0.99658	0.09812
3.00	0.96355	0.57461
4.00	0.90837	3.78113

Table 2 Rate constant for anhydride formation in Eudragit L-100 film at different temperatures by using $n = 1.85$ and equation (4)

Temperature (°C)	Correlation coefficient	$k_{(T)}$ (min^{-1})
200	0.99729	0.07622
190	0.95662	0.02871
180	0.99521	0.01062
160	0.99959	0.00051

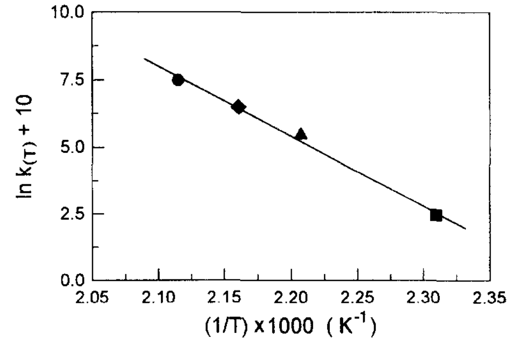

Figure 5 A plot of $\ln k_{(T)}$ against $1/T$ for anhydride formation in Eudragit L-100 film. Symbols as in *Figure 4*

equations (3) and (4) and to obtain the $k_{(T)}$ value. The best n value is obtained by selecting the reaction order giving the highest correlation coefficient of the linear least-squares fit of equations (3) and (4), as shown in *Table 1*. From *Table 1*, the best value of n is 1.85 with the best correlation coefficient, which might be considered as a second-order reaction. The exact rate constant for the anhydride formation in Eudragit L-100 films at different temperatures, by using $n = 1.85$ and equation (4), is listed in *Table 2*, in which all the reactions revealed a good correlation coefficient. The activation energy (E_a) of anhydride formation can be determined by an Arrhenius equation as follows:

$$k_{(T)} = A\exp(-E_a/RT) \qquad (5)$$

where A is a constant known as the frequency factor, R is the gas constant and T is the absolute temperature. A plot of $\ln k_{(T)}$ against $1/T$ was obtained, as shown in *Figure 5*. A linear relationship ($\ln k_{(T)} = -25790.6/T + 52.12$, $r = 0.9957$) was obtained and the activation energy was calculated from the slope (E_a/R). The activation energy is 51.25 kcal mol^{-1}. This suggests that the anhydride formation in Eudragit L-100 films needs an activation energy of 51.25 kcal mol^{-1} to perform its polycondensation under second-order reaction.

CONCLUSIONS

The method of reflectance *FT*i.r./d.s.c. microspectroscopy is a potential tool for the investigation of anhydride formation in Eudragit L polymer, and for obtaining information about the kinetics and the reaction order of simple polymer condensation.

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