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Study of a theophylline–Eudragit L mixture using a combined system of microscopic Fourier-transform infrared spectroscopy and differential scanning calorimetry

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Abstract

A newly developed system of microscopic Fourier-transform infrared spectroscopy combined with differential scanning calorimetry was used to determine simultaneously the thermoresponsive IR spectral change of a physical mixture or a cast film of theophylline and Eudragit L-100 by means of a three-dimensional plot. The results indicated that this newly developed system was quick, simple and useful for determining the glass transition of the physical mixture or cast film. Because of the hydrogen bonding occurring in the cast film, the glass transition temperature of the cast film was higher than that of the physical mixture or Eudragit L-100 alone. An interaction between theophylline and Eudragit L-100 was also found in the physical mixture during DSC heating. Moreover, we found that the formation of an acid anhydride by a crosslinking process also took place in Eudragit L-100 polymer at elevated temperature.

Keywords: Coupled technique; DSC; Eudragit L; FTIR; Interaction; Theophylline

1. Introduction

The incorporation of a hydrophobic drug into a water-soluble polymer may enhance dissolution of the drug through dispersion in the system. This enhancement

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in drug release has been attributed to different mechanisms, such as the formation of a high-energy complex, molecular dispersion, hydrogen bonding or a coacervate [1–4]. The same approach can be used to delay the release of a water-soluble drug from a hydrophilic or hydrophobic polymer by a diffusion mechanism, thereby resulting in a slow or sustained release of the drug [5–8]. Lin and coworkers [9–11] have found that the formation of hydrogen bonding between a drug and Eudragit resins could delay drug release because of the drag effect.

Indomethacin, warfarin and piroxicam have been found to interact with Eudragit resins by hydrogen bonding and to form a molecularly dispersed drug-loaded polymeric film [9–11]. The physico-chemical properties of these drug-loaded films have generally been investigated within a short time after manufacture, but the effect of ageing on these drug-loaded films is important although less often mentioned. An accelerated study over a short period of time may afford this information. A newly developed system of microscopic Fourier-transform infrared (FTIR) spectroscopy with differential scanning calorimetry (DSC) has been used simultaneously to determine the correlation between the thermal response and the chemical structural changes of samples. Lin and coworkers used this combined system for the accelerated determination of the phase transformation of indomethacin polymorphs and anthraquinone-2-carboxylic acid solvate [12,13], the lipid and protein thermotropic transition of porcine stratum corneum [14], the curing kinetics of silicone elastomer [15] and the protective ability of microencapsulated squid oil [16] within a short period of time. It was of great interest to us to acceleratively investigate a drug-loaded film by this newly developed microscopic FTIR/DSC system. The objective of the present investigation was to study the thermoresponsive properties in physical mixtures and cast films of theophylline and Eudragit L by this microscopic FTIR/DSC system.

2. Materials and methods

2.1. Materials

Anhydrous theophylline was purchased from Delta Synthetic Co. Ltd., Taiwan. The pulverized theophylline (< 100 μm) was used. Eudragit L-100 (< 100 μm) was kindly supplied by Rohm Pharma, Germany. The 95% ethanol was of analytical reagent grade.

2.2. Preparation of test samples

2.2.1. Physical mixture

Theophylline and Eudragit L-100 powder previously weighed out in the ratio 3:0.5 were mixed well for 5 min in a mortar. The mixture was stored in a sealed container for further study.

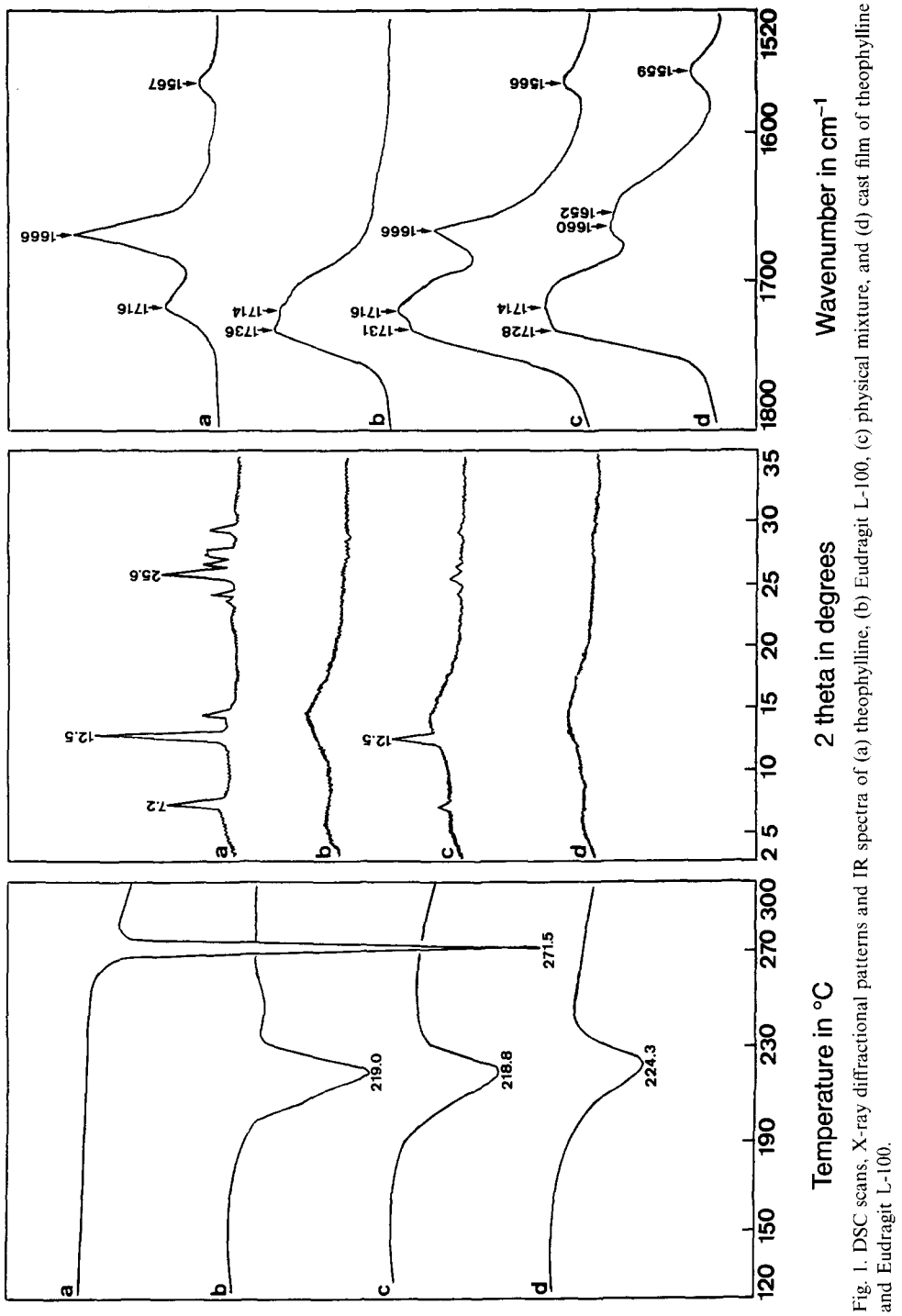

Fig. 1. DSC scans, X-ray diffractional patterns and IR spectra of (a) theophylline, (b) Eudragit L-100, (c) physical mixture, and (d) cast film of theophylline and Eudragit L-100.

2.2.2. Cast film

A specific amount of mixed theophylline–Eudragit L-100 powder (weight ratio 3:0.5) was completely dissolved in 95% ethanol. This ethanolic drug solution was cast on a glass plate. The ethanol was evaporated at room temperature to form an opaque film, which was vacuum dried for 24 h at 25°C and stored in a sealed container until used.

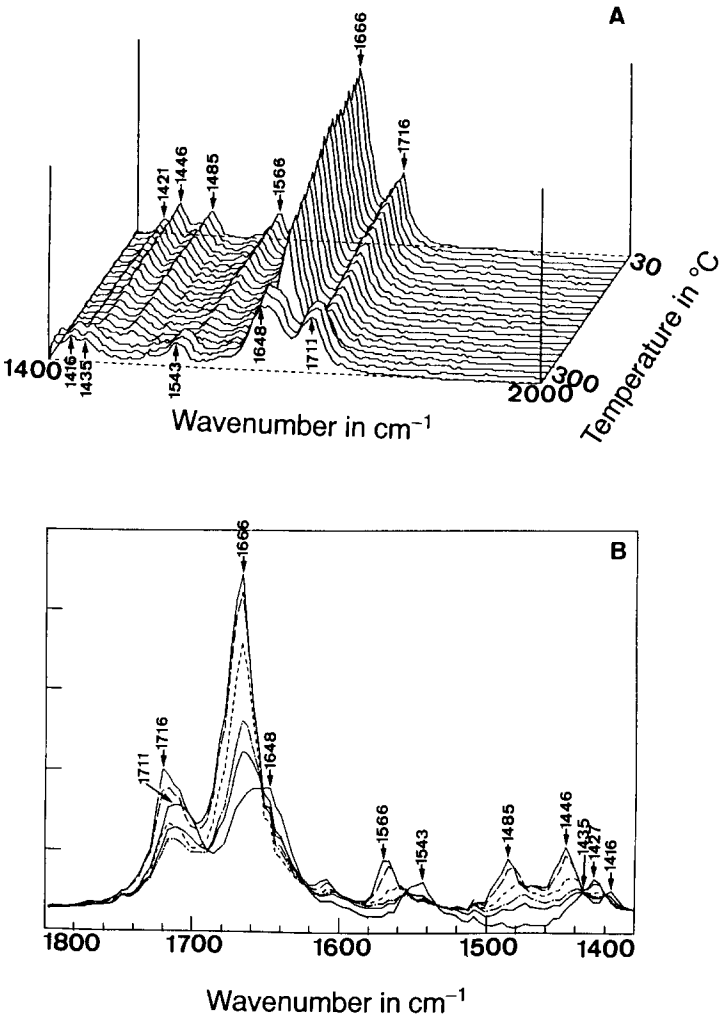

Fig. 2. (A) Three-dimensional plot of IR spectra of theophylline with respect to the temperature, and (B) temperature-dependent absorption spectra.

2.3. Analysis of raw materials and test samples

Theophylline, Eudragit L-100, the physical mixture and the cast film of theophylline–Eudragit L-100 were examined using a differential scanning calorimeter (DSC-910, TA Instruments Inc., USA) and/or a thermogravimetric analyser (TGA-951, Du Pont, USA) at a scanning rate of 10°C min^{-1} under flowing N_2 gas; a powder X-ray diffractometer (Philips PW-1840, USA) with Cu Kα radiation at 35 kV and 20 mA; and a Fourier-transform infrared (FTIR) spectrophotometer (Micro FTIR-200, Jasco, Japan) by the KBr disc method.

2.3.1. FTIR microscopy with thermal analysis

Each sample was sealed between KBr discs (6 mm) by hydraulic pressing. The KBr disc was placed in a DSC microscopy cell (FP 84, Mettler, Switzerland). The DSC cell was then placed in the Micro FTIR-200 instrument equipped with an MCT detector. The position and focus of the sample were adjusted under the microscope. The temperature of the DSC microscopy cell was controlled by a central processor (FT80HT, Mettler, Switzerland). During each experiment, the sample disc was equilibrated at the starting temperature of 30°C for ≈ 3 min and then heated. The heating rate for the DSC cell was set at 10°C min^{-1}. The three-dimensional IR spectra were recorded while the disc was heated in a DSC microscopy cell [12–16].

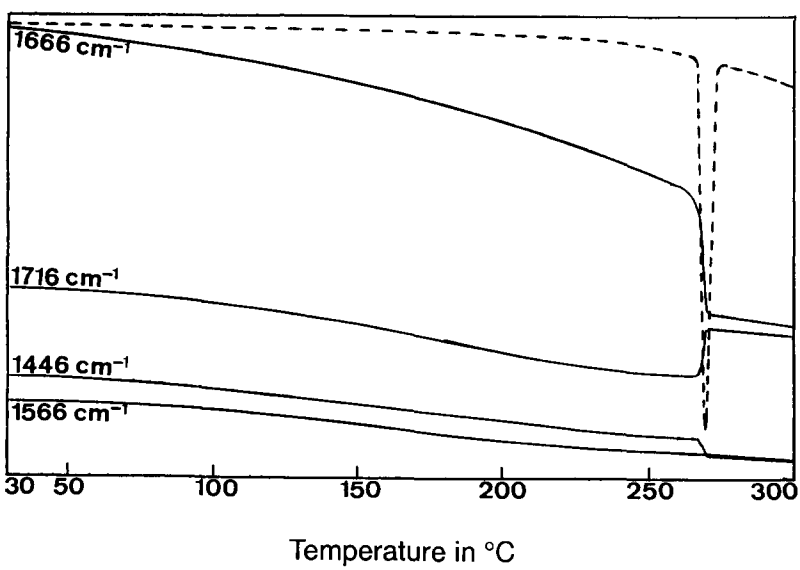

Fig. 3. Changes in intensity for several specified IR peaks of theophylline with respect to temperature.

3. Results and discussion

Fig. 1 shows the DSC curves, X-ray diffraction patterns and IR spectra of theophylline, Eudragit L-100, their physical mixture and the cast film of theophylline–Eudragit L-100 (weight ratio 3:0.5). Obviously, the endothermic peaks at 271 and 219°C are due to the fusion of theophylline and the crosslinking formation of Eudragit L-100, respectively. The crosslinking process of the polymer may give a broad endothermic peak in the DSC curve [18,19]. X-ray diffraction patterns indicate that theophylline is in the crystalline state but Eudragit L-100 is amorphous. The IR absorption peaks at 1716 and 1666 cm^{-1} for theophylline were

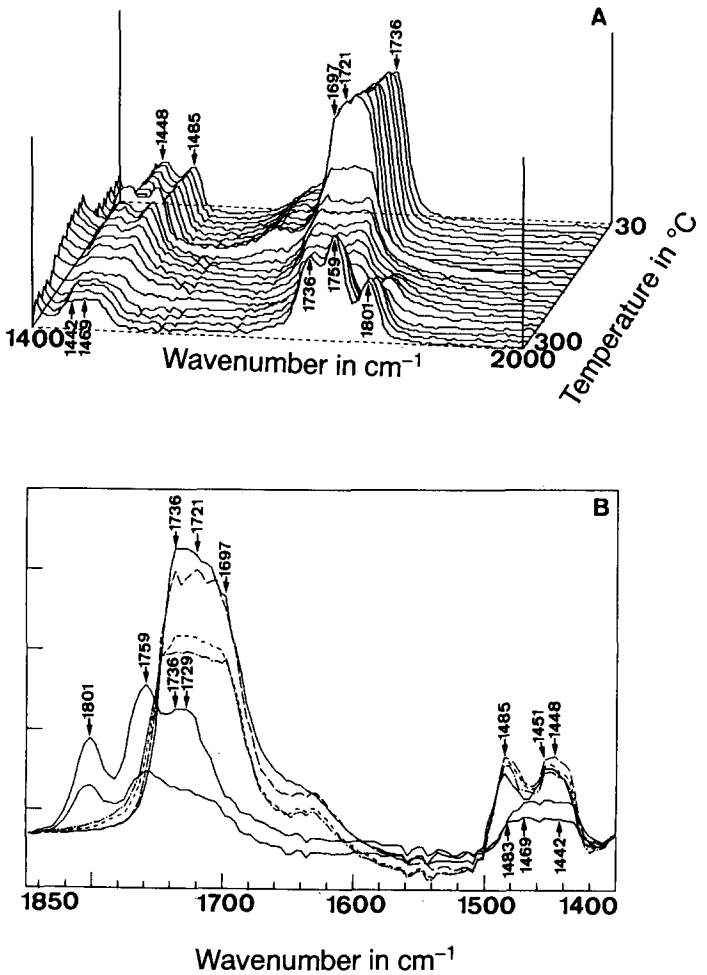

Fig. 4. (A) Three-dimensional plot of IR spectra of Eudragit L-100 with respect to the temperature, and (B) temperature-dependent absorption spectra.

assigned to the C=O stretching vibration for carbonyl groups and the peak at 1566 cm^{-1} was attributed to the stretching vibration of the imine group of theophylline. The IR peaks at 1736 and 1714 cm^{-1} were respectively due to the esterified carboxyl and carboxylic acid groups of Eudragit L-100. It is clear that the DSC curve of the physical mixture of theophylline and Eudragit L is almost the same as that of Eudragit L, but the DSC curve of theophylline did not appear. The small amount of theophylline previously melted and dispersed in the fused Eudragit L polymer might be responsible for this result. The X-ray diffraction pattern and the IR spectrum of this physical mixture corresponded to the additive patterns of the raw materials. However, the DSC scan, X-ray diffraction pattern and IR spectrum of the cast film were different from those of the physical mixture. The DSC endothermic peak for the cast film appeared at 224.3°C and the X-ray diffraction pattern was that of an amorphous material. The IR peak at 1666 cm^{-1} assigned to the carbonyl stretching vibration of theophylline shifted to 1660 cm^{-1} and the peak at 1566 cm^{-1} due to the stretching vibration of imine was shifted to 1559 cm^{-1}. Moreover, a new peak at 1652 cm^{-1} appeared in the spectrum of the cast film. These shifting phenomena of the DSC endothermic peak (from 219 to 224°C) and the IR spectrum for the cast film might be attributable to the formation of hydrogen bonding between theophylline and Eudragit L after solvent evaporation. The amorphous X-ray diffraction pattern also implied that the theophylline was molecularly dispersed in the Eudragit L film.

Fig. 2 shows the three-dimensional plot of the FTIR spectra of theophylline between 1400 and 2000 cm^{-1} with respect to temperature. It is evident from the figure that the IR peak intensity of theophylline becomes gradually weaker with an

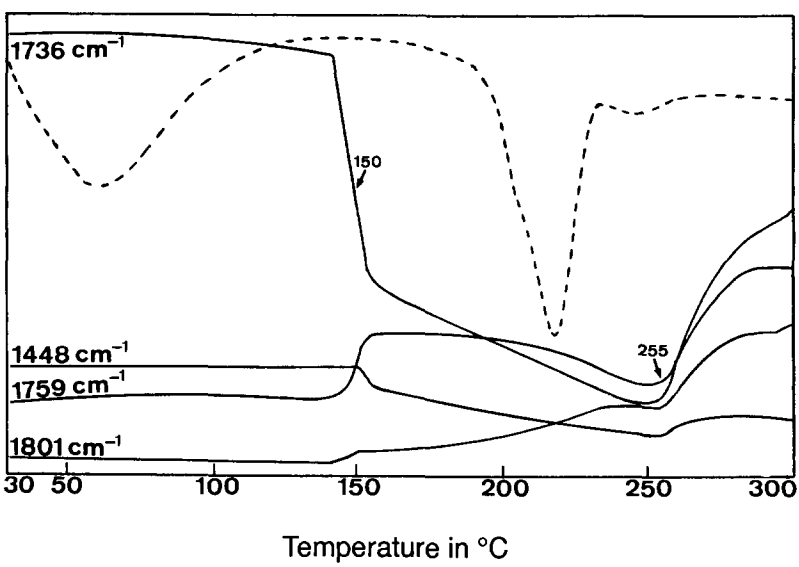

Fig. 5. Changes in intensity for several specified IR peaks of Eudragit L-100 with respect to temperature.

increase in temperature. The decrease in intensity might be due to destruction of the crystalline structure of theophylline at higher temperatures. Moreover, the decreased cooperative effects and the weakened vibrational coupling in the theophylline structure were also related to this intensity decrease phenomenon [19]. Beyond the melting point (271°C) of theophylline, TGA data indicated that theophylline was significantly decomposed, and new IR peaks at 1711, 1648 and 1543 cm^{-1} for the degraded products were found. Fig. 3 shows the temperature-dependent peak intensity of four specified IR peaks. These peak intensities gradually decreased with increase in the temperature. Once beyond the melting point of

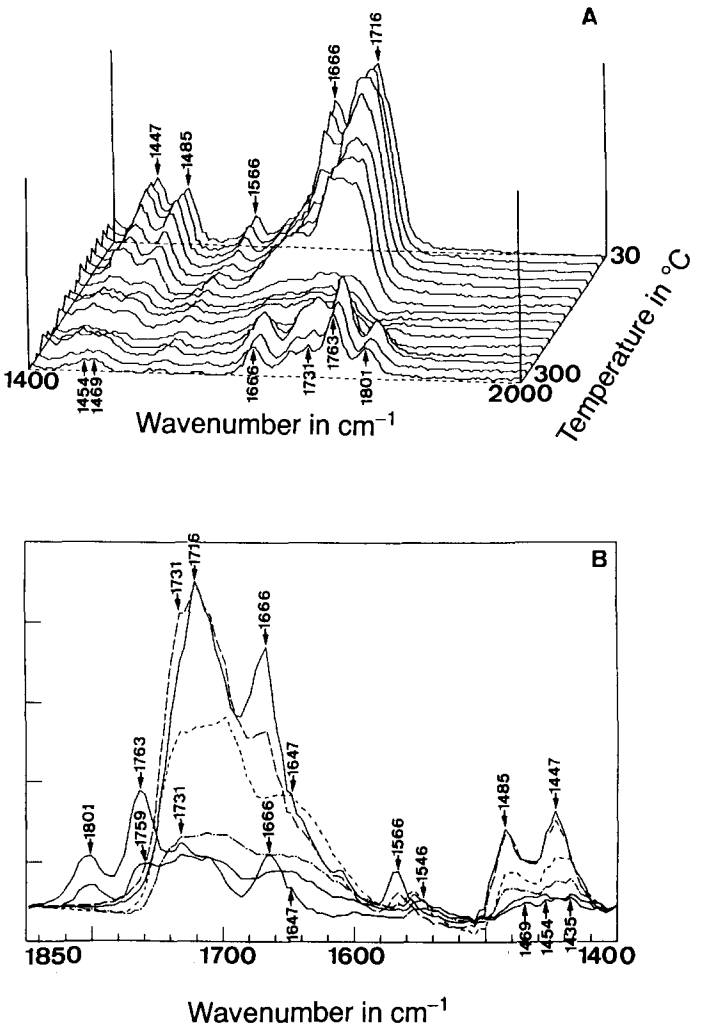

Fig. 6. (A) Three-dimensional plot of IR spectra of the physical mixture of theophylline and Eudragit L-100 with respect to temperature, and (B) temperature-dependent absorption spectra.

theophylline, the intensity of the specified peaks was clearly changed; in particular, the carbonyl group at the 6-position in theophylline structure was easily decomposed, leading to a large decrease in the peak intensity at 1666 cm^{-1}.

The three-dimensional plot of the IR spectra of Eudragit L-100 between 1400 and 2000 cm^{-1} with respect to temperature is shown in Fig. 4. Apparently, the characteristic bands for C=O vibrations of the esterified carboxyl groups at 1736 cm^{-1} and of the carboxylic acid groups at 1714 cm^{-1} caused by intermolecular hydrogen bonding and those of the CH_2 and/or CH_3 bending vibrations of Eudragit L-100 become weaker with increasing temperature. At higher temperatures, near 300°C, the TGA data did not indicate decomposition. However, two additional peaks corresponding to the C=O vibrations were found at 1801 and

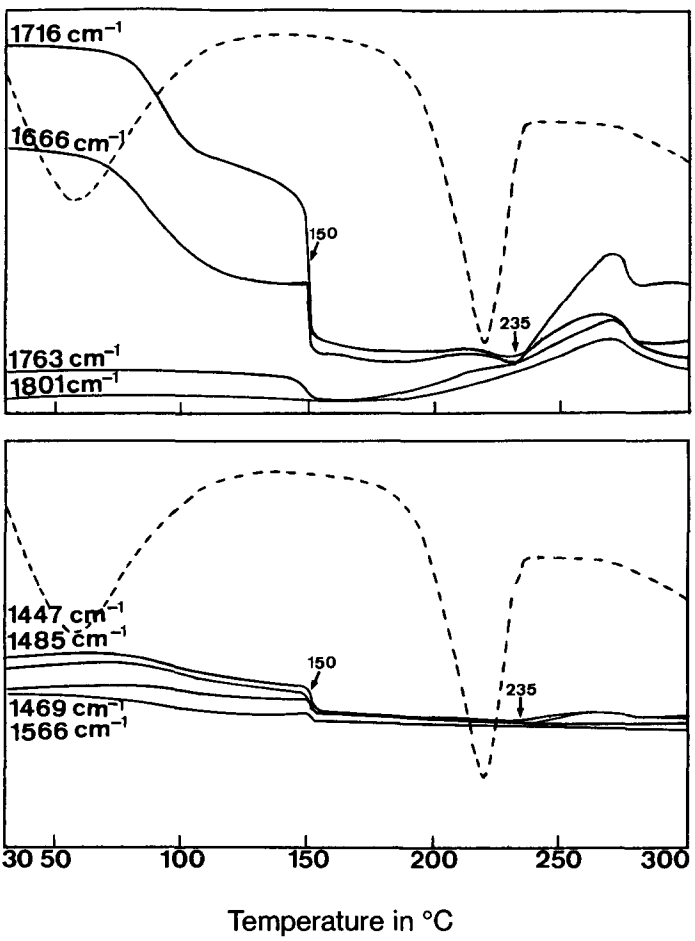

Fig. 7. Changes in intensity for several specified IR peaks of the physical mixture of theophylline and Eudragit L-100 with respect to temperature.

1759 cm^{-1}. Because Eudragit L-100 is a copolymer of methacrylic acid and methyl methacrylate, it might undergo dissociation of the intermolecular hydrogen bonding and then form the acid anhydride by crosslinking at higher temperature [20], resulting in an increase in absorption frequency at both 1801 and 1759 cm^{-1}. Fig. 5 shows the temperature dependence of the absorption of the specified IR peaks. Two points of inflection appeared, at ≈ 150 and ≈ 255°C. The first inflection at 150°C could be related to the glass transition temperature of Eudragit L-100, as this temperature is consistent with the glass transition temperature of Eudragit L-100 after a quenching process [21]. The finding also suggests that the FTIR/DSC system can easily be used to determine the glass transition temperature of a polymer without quenching. The second inflection at 255°C might be a complex temperature response: beyond 255°C all IR peak absorptions were increased and shifted to

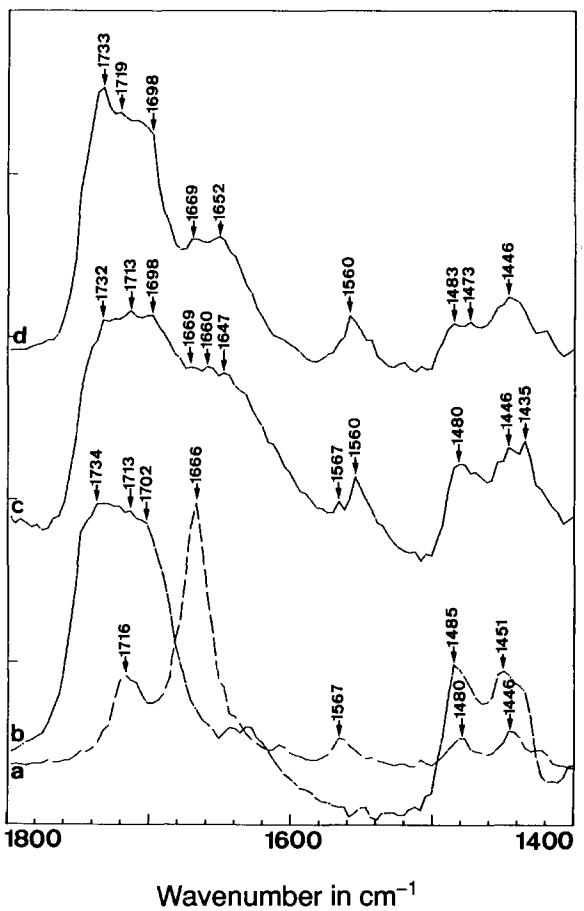

Fig. 8. IR spectra of (a) 80°C-heated theophylline, (b) 150°C-heated Eudragit L-100, (c) 150°C-heated physical mixture, and (d) cast film of theophylline and Eudragit L-100, obtained from the corresponding three-dimensional plots.

higher wavenumber, suggesting that dissociation of the intermolecular hydrogen bonding and/or formation of acid anhydride was more complete in the Eudragit L polymer. The change of Eudragit L-100 at this second inflection temperature will be studied in future work.

The thermodependent 3-dimensional plot of IR spectra for the physical mixture of theophylline and Eudragit L-100 (weight ratio 3:0.5) is illustrated in Fig. 6. It is evident that the thermodependent change in the physical mixture is almost a summation of the respective changes of theophylline and Eudragit L. The glass transition temperature of this physical mixture also appeared at 150°C, as shown in

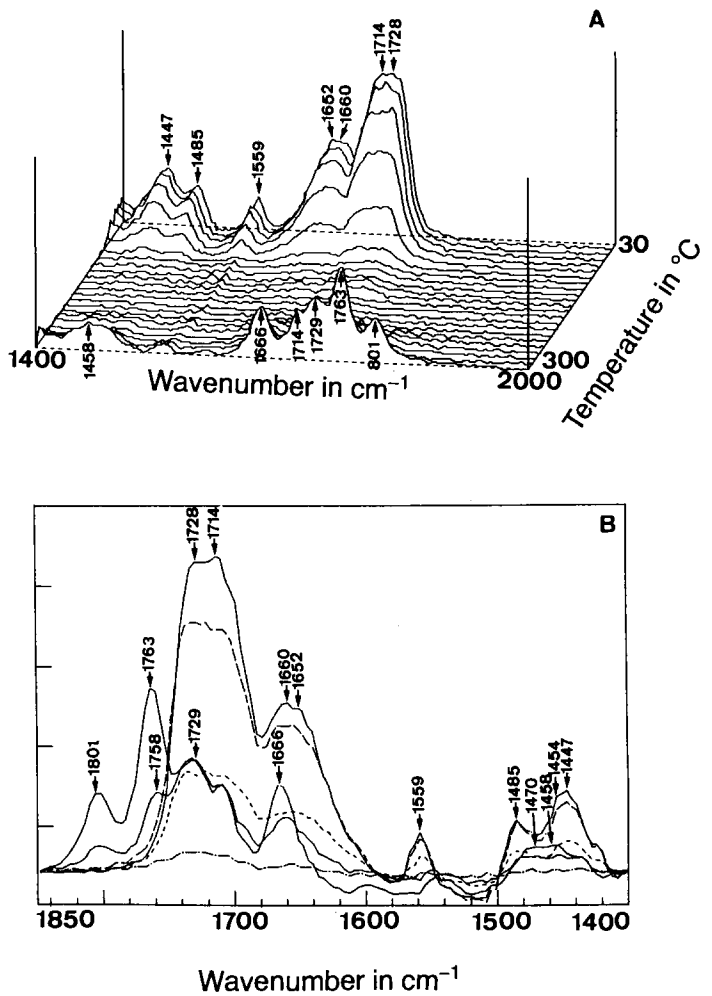

Fig. 9. (A) Three-dimensional plot of IR spectra of the cast film of theophylline and Eudragit L-100 with respect to temperature, and (B) temperature-dependent absorption spectra.

Fig. 7, which is the same as the glass transition temperature of Eudragit L-100. However, Eudragit L revealed a second inflection temperature at 255°C related to dissociation of the intermolecular hydrogen bonding and/or formation of acid anhydride in the Eudragit L polymer. In contrast, the second inflection temperature for the physical mixture was 235°C. The decrease in this temperature from 255 to 235°C might be attributable to the Eudragit L previously melted and co-fused with theophylline. If the melted theophylline interacted with a portion of the Eudragit L, the non-interacted amount of Eudragit L would be reduced, resulting in a decrease in this second inflection for Eudragit L to lower temperature. Fig. 8(c) serves to confirm the interaction of theophylline and Eudragit L caused by DSC heating. We find that the peak at 1567 cm^{-1} assigned to the imine of theophylline

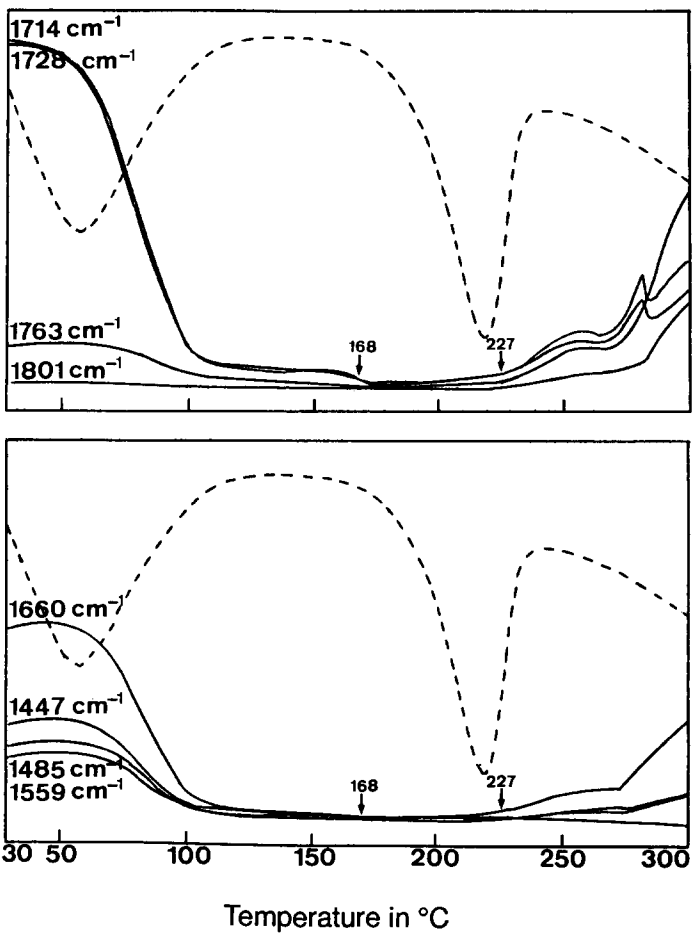

Fig. 10. Changes in intensity for several specified IR peaks of the cast film of theophylline and Eudragit L-100 with respect to temperature.

shifts to 1560 cm^{-1} for the physical mixture of theophylline and Eudragit L after thermal treatment (Fig. 8(c)), a similar effect to that in the IR spectra of the cast film (Fig. 8(d)). Although the cast film prepared from theophylline and Eudragit L showed a different IR spectrum at 30°C as compared with the physical mixture (Fig. 1), owing to the formation of hydrogen bonding between theophylline and Eudragit L in the cast film, the thermoresponsive 3-dimensional IR plot for the cast film, as shown in Fig. 9, was similar to that of the physical mixture (Fig. 6). Fig. 10 shows the thermodependent IR absorption of several specified peaks for the cast film. Evidently the glass transition temperature of the cast film is 168.2°C, which is higher than that of the physical mixture ($T_g = 150.2$°C). The occurrence of hydrogen bonding between theophylline and Eudragit L in the cast film could cause a fall in polymer chain mobility, resulting in a rise of the glass transition temperature of the polymer [21]. The second inflection temperature of the cast film is reduced to 227°C, as compared with that of the physical mixture (235°C) or Eudragit L-100 polymer (255°C). As hydrogen bonding occurred between theophylline and a certain amount of the Eudragit L-100, the residual amount of Eudragit L decreased, and this might be responsible for the lower second inflection temperature.

4. Conclusions

In conclusion, the newly developed combined system of microscopic FTIR spectroscopy and DSC is quick, simple and useful for determining the glass transition and thermodependent dissociation temperatures of a physical mixture or cast film of theophylline and Eudragit L-100. The thermoresponsive IR spectral change of the sample can be easily obtained.

References

[1] A.P. Simonelli, S.C. Metha and W.I. Higuchi, Dissolution rates of high energy polyvinylpyrrolidone–sulphathiazole coprecipitates, J. Pharm. Sci., 58 (1969) 538–549.
[2] W.L. Chiou and S. Riegelman, Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci., 60 (1971) 1281–1303.
[3] E. Shefter and K.C. Cheng, Drug–polyvinylpyrrolidone dispersions. A differential scanning calorimetric study, Int. J. Pharm., 6 (1980) 179–182.
[4] H. Sekigawa, J. Fujiwara, T. Nagamma, M. Nakano and T. Arita, Dissolution behaviors and gastrointestinal absorption of phenytoin in phenytoin–polyvinylpyrrolidone coprecipitates, Chem. Pharm. Bull., 27 (1979) 1223–1230.
[5] R. Bodmeier and O. Paeratakul, Drug release from laminated polymeric films prepared from aqueous latexes, J. Pharm. Sci., 79 (1990) 32–36.
[6] M.R. Jenquin, S.M. Liebowitz, R.E. Sarabia and J.W. McGinity, Physical and chemical factors influencing the release of drugs from acrylic resins films, J. Pharm. Sci., 79 (1990) 811–816.
[7] M.R. Jenquin and J.W. McGinity, Characterization of acrylic resin matrix films and mechanisms of drug–polymer interactions, Int. J. Pharm., 101 (1994) 23–34.
[8] S.Y. Lin, S.J. Hou and R.I. Perng, Effect of direct compression or spray-dried encapsulation on the salbutamol release from hydrophilic matrix tablets, Chin. Pharm. J., 44 (1992) 153–160.

[9] S.Y. Lin and R.I. Perng, Solid-state interaction studies of drugs/polymers: I. Indomethacin/Eudragit E, RL or S resins, STP Pharma Sci., 3 (1993) 465–471.
[10] S.Y. Lin, C.L. Cheng and R.I. Perng, Solid state interaction studies of drugs/polymers: II. Warfarin–Eudragit E, RL or S resins. Eur. J. Pharm. Sci., 1 (1994) 313–322.
[11] S.Y. Lin, C.J. Lee and Y.Y. Lin, Drug–polymer interaction affecting the mechanical properties, adhesion strength and release kinetics of piroxicam-loaded Eudragit E films plasticized with different plasticizers, J. Control Rel., in press.
[12] S.Y. Lin, Isolation and solid-state characteristics of a new crystal form of indomethacin, J. Pharm. Sci., 81 (1992) 572–576.
[13] S.Y. Tsai, S.C. Kuo and S.Y. Lin, Physicochemical characterization of 9,10-anthraquinone-2-carboxylic acid, J. Pharm. Sci., 82 (1993) 1250–1254.
[14] S.Y. Lin, R.C. Liang and T.C. Lin, Lipid and protein thermotropic transition of porcine stratum corneum by microscopic calorimetry and infrared spectroscopy. J. Chin. Chem. Soc., 41 (1994) 425–429.
[15] S.Y. Lin, W.J. Tsay, Y.L. Chen and C.J. Lee, Application of a new micro FTIR/DSC technique to the study of curing kinetics of silicone elastomer, J. Controlled Release, 31 (1994) 277–282.
[16] S.Y. Lin, L.S. Hwang and C.C. Lin, Thermal analyser and micro FTIR/DSC system used to determine the protective ability of microencapsulated squid oil, J. Microencapsulation, in press.
[17] R. Kay and A.R. Westwood, DSC invesigations on condensation polymer — I: Analysis of the curing process, Eur. Polym. J., 11 (1995) 25–30.
[18] J.F. Rabek, Thermal analysis of polymers, in J.F. Rabek (Ed.), Experimental Methods in Polymer Chemistry, John Wiley&Sons, New York, 1980, pp. 549–581.
[19] W.A. Bueno and S.G. Ribeiro, The effect of temperature on the infrared spectra of H-bond complexes, J. Mol. Struct., 273 (1992) 1–9.
[20] L.G. Wade, Derivatives of carboxylic acids, I: Structure, properties, acid halides, anhydrides, in L.G. Wade (Ed.), Organic Chemistry, Prentice-Hall International, Englewood Cliffs, NJ, 1987, pp. 1018–1060.
[21] S.Y. Lin, C.M. Liao and R.C. Liang, Use of microscopic FTIR/DSC combined system for the study of glass transition temperature of polymers, Polymer J., 27 (1995) 201–204.
[22] A. Okhamafe and P. York, Thermal characterization of drug/polymer and excipient/polymer interactions in some film coating formulations, J. Pharm. Pharmacol., 41 (1989) 1–6.