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COMMUNICATION

Enhanced Dissolution of Ursodeoxycholic Acid from the Solid Dispersion

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ABSTRACT

Solid dispersions of a very slightly water-soluble drug, ursodeoxycholic acid (UDCA), were prepared using urea, mannitol, and PEG 6000 as a carrier, and the solubility of UDCA was determined in water-ethanol (1:1) mixed solvent as a function of UDCA-carrier ratio. The solubility of UDCA was slightly improved when urea or PEG 6000 was used as a carrier. The powder x-ray diffraction measurements revealed that UDCA did not exist in the crystalline state in the solid dispersions. Differential scanning calorimetry (DSC) studies showed that UDCA was able to dissolve in the melt of urea, mannitol, and PEG 6000. The effect of carriers of solid dispersions on the UDCA dissolution rate was examined. The dissolution rate of UDCA was markedly increased from the solid dispersions of urea, PEG 6000, and mannitol, respectively.

INTRODUCTION

Ursodeoxycholic acid (UDCA) has been used for the dissolution of radiolucent gallstones that were formed predominantly from cholesterol (1–3), and can also be useful in the treatment of dyspepsia symptoms and biliary pain (4–7). Because UDCA is practically insoluble in water (8), improvement of the dissolution of UDCA from its oral solid dosage form should be an important issue to enhance the bioavailability (9).

Amorphization is a conventional methodology for enhancing the dissolution properties, and various techniques have been developed to obtain amorphous state of medicinals. These include grinding of drug with certain additives such as porous powders (10–12). The use of solid dispersion has also been investigated (13–15) to

improve the dissolution properties and bioavailability of poorly water-soluble drug. The present work has been undertaken to develop a solid dispersion of UDCA in water-soluble carriers (polyethylene glycol 6000, urea, and mannitol) in order to improve the dissolution behavior of UDCA.

MATERIALS AND METHODS

Materials

UDCA was obtained from Tokyo Tanabe Co. Ltd., Japan. Polyethylene glycol (PEG) 6000 was purchased from Wako Pure Chemical Industry, Japan. Urea and mannitol were purchased from Nacalai Tesque Inc., Japan.

Preparation of UDCA Solid Dispersions

Solid dispersions of UDCA with each of PEG 6000, urea, and mannitol were prepared at weight ratios of 1:1, 1:4, and 1:19 (drug:carrier), respectively. After a carrier material was completely melted in a thermostated oil bath, UDCA was dissolved and then solidified by being poured onto a glass petri dish stored on an ice bath. After the resulting solid was cooled, it was kept in vacuo. After the powdered sample was pulverized, it was fractionated in the particle size range of 60–200 mesh by sieving.

Powder X-ray Diffraction (XRD) Analysis

The powder XRD was carried out on a Rigaku Denki 2027 diffractometer (CuKα, 30 kV, 5 mA, with a scintillation counter, scanning speed 4°/min.)

Differential Scanning Calorimetry (DSC) Studies

A DuPont 9900 thermal analyzer was used. A 1.5-mg sample was sealed in an aluminum pan. The measurements were carried out under nitrogen gas flow of 60 ml/min and at a heating rate of 10°C/min. An empty pan was used as a reference.

Infrared Spectroscopy

IR spectra were obtained by KBr disk method using a Nicolet 5ZDX Fourier-transform infrared (FTIR) spectrometer. KBr disks were prepared using a hydrostatic press at a thrust of 5 tons/cm^2 for 5 min.

Solubility Measurement

An excess amount of UDCA was placed into a 20-ml L-shaped glass test tube containing various concentrations of each carrier in 10 ml of 1:1 ethanol–water mixture. All of the test tubes were closed with stopper and cover-sealed with cellophane membrane to avoid solvent loss. The suspension was incubated and shaken for 24 hr at 37°C in a water bath. After equilibrium, the suspension was quickly filtered through a 1.2-μm membrane filter. After the color reaction, the concentration of dissolved UDCA was determined spectrophotometrically at a wavelength of 525 nm (16).

Dissolution Studies

Dissolution studies were conducted using USP XXIII apparatus no. 2 for dissolution testing. A powder sample containing 250 mg of UDCA was compressed under 450 kg/cm^2 into a 10-mm-diameter flat face tablet. The tablet was fixed to the bottom of the beaker containing 100 ml of 1:1 ethanol–water mixture at 37°C as a medium. The side of the tablet was sealed by paraffin to allow only the top surface to contact the medium throughout the dissolution experiment. The paddle rotation speed was adjusted to 100 rpm. A 500-μl sample of the solution was taken out periodically, and the same amount of solvent at the same temperature was replaced. The amount of UDCA dissolved was determined by the color reaction method (16). The test was performed in triplicate.

RESULTS AND DISCUSSION

The XRD and Thermal Behavior of UDCA Solid Dispersions

The powder XRD patterns of UDCA–PEG 6000, UDCA–urea, and UDCA–mannitol solid dispersions are shown in Figs. 1–3, respectively, in drug:carrier ratios of 1:1, 1:4, and 1:19. In the diffractograms, all diffraction peaks were due to carrier crystals and no diffraction peaks of UDCA in the solid dispersions were observed. This indicates that the amorphous state of UDCA was formed in the solid dispersions below 50%

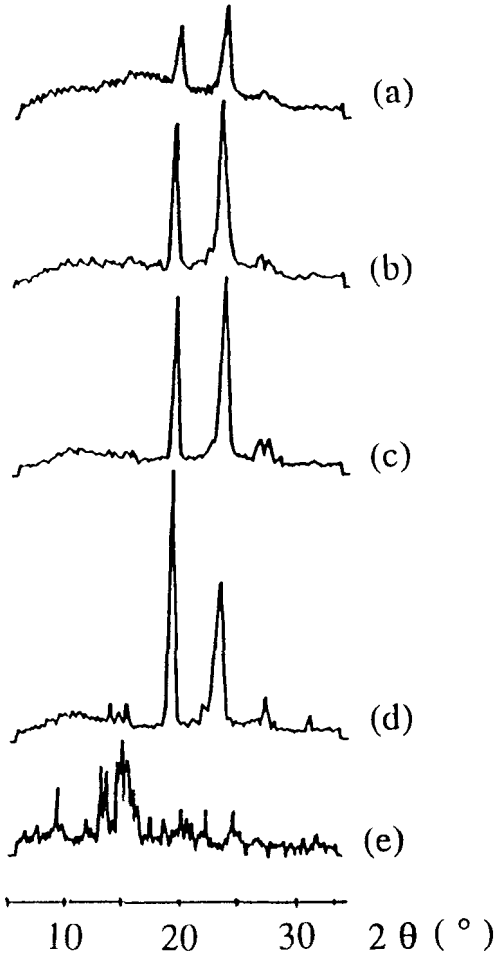

Figure 1. Powder XRD patterns of UDCA–PEG 6000 (1:1) solid dispersion (a), UDCA–PEG 6000 (1:4) solid dispersion (b), UDCA–PEG 6000 (1:19) solid dispersion (c), pure PEG 6000 (d), and pure UDCA (e).

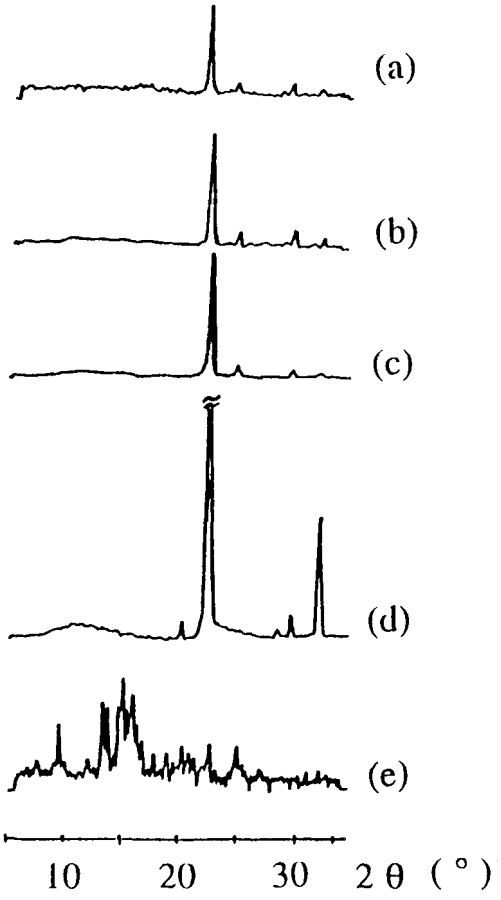

Figure 2. Powder XRD patterns of UDCA–urea (1:1) solid dispersion (a), UDCA–urea (1:4) solid dispersion (b), UDCA–urea (1:19) solid dispersion (c), pure urea (d), and pure UDCA (e).

UDCA concentration. Because a higher drug content is suitable for a practical use, the solid dispersions of 1:1 ratio were chosen for further studies.

The DSC thermograms of UDCA solid dispersions (1:1 weight ratio) with various carriers are shown in Fig. 4. On the DSC curves of pure UDCA, PEG 6000, urea, and mannitol, the melting point of each component appeared at 205.0, 63.5, 136.9, and 168.7°C, respectively. The DSC thermograms of UDCA–PEG 6000 and UDCA–urea solid dispersion showed endothermic peaks at 56.1 and 132.4°C, respectively, presumably due to the melting of PEG 6000 and urea crystals which were highly disordered by the incorporation of UDCA molecules. The small broad peaks were found at 191.6 and 150.7°C for UDCA-PEG 6000 and UDCA–urea solid dispersion, respectively. After the melting of carrier, it might be possible that the residual small crystallites of UDCA, which were too small to be detected by XRD, melted into the media at these temperatures. The thermogram of UDCA–mannitol solid dispersion, however, showed no UDCA endothermic peak but did exhibit the endothermic peak due to the fusion of mannitol at 167.5°C. This result indicates that there should be no crystal of UDCA in the UDCA–mannitol solid disper-

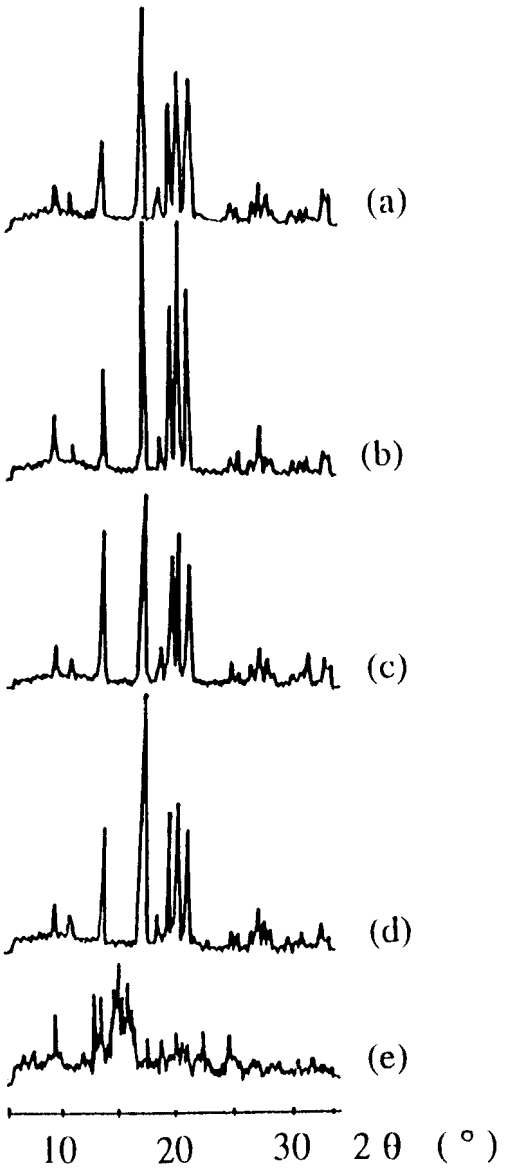

Figure 3. Powder XRD patterns of UDCA–mannitol (1:1) solid dispersion (a), UDCA–mannitol (1:4) solid dispersion (b), UDCA–mannitol (1:19) solid dispersion (c), pure mannitol (d), and pure UDCA (e).

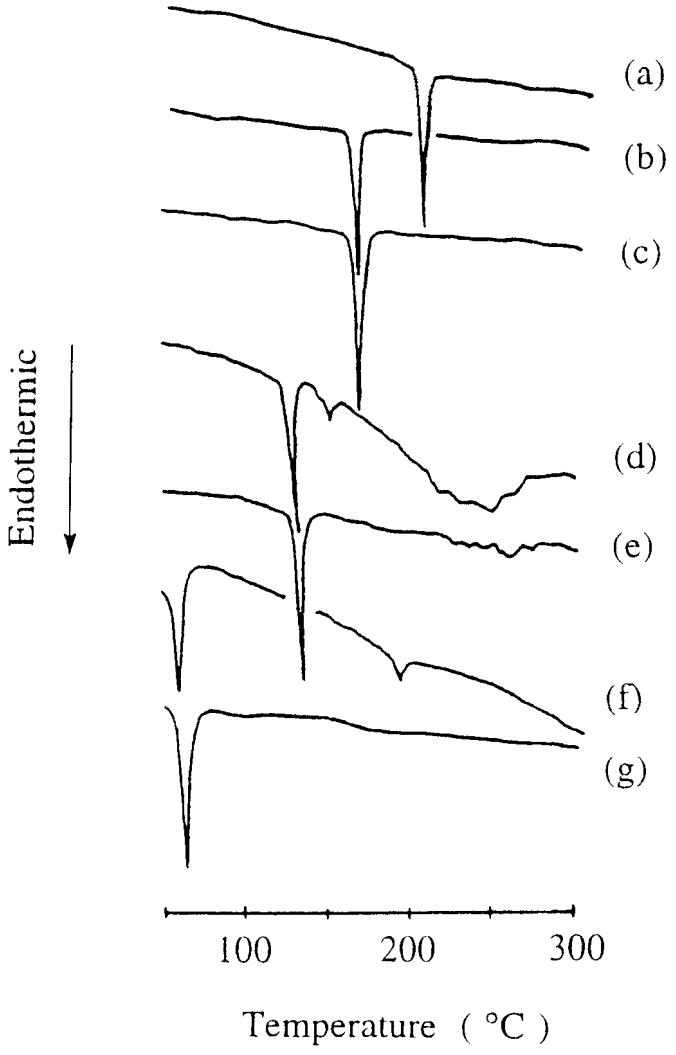

Figure 4. DSC thermagrams of pure UDCA (a), UDCA–mannitol (1:1) solid dispersion (b), pure mannitol (c), UDCA–urea (1:1) solid dispersion (d), pure urea (e), UDCA–PEG 6000 (1:1) solid dispersion (f), and pure PEG 6000 (g).

sion. In the mannitol system, the result was in agreement with the XRD result that UDCA could be dispersed in an amorphous state. The DSC results indicate that the presence of PEG 6000, urea, and mannitol would affect the crystalline state of UDCA and might affect the dissolution of UDCA in the solid dispersions.

The IR spectra in the 1500–1800 cm^{-1} region of UDCA solid dispersions are shown in Fig. 5. The pure UDCA showed the carbonyl stretching absorption band at 1708 cm^{-1}. The solid dispersions of UDCA–manni-

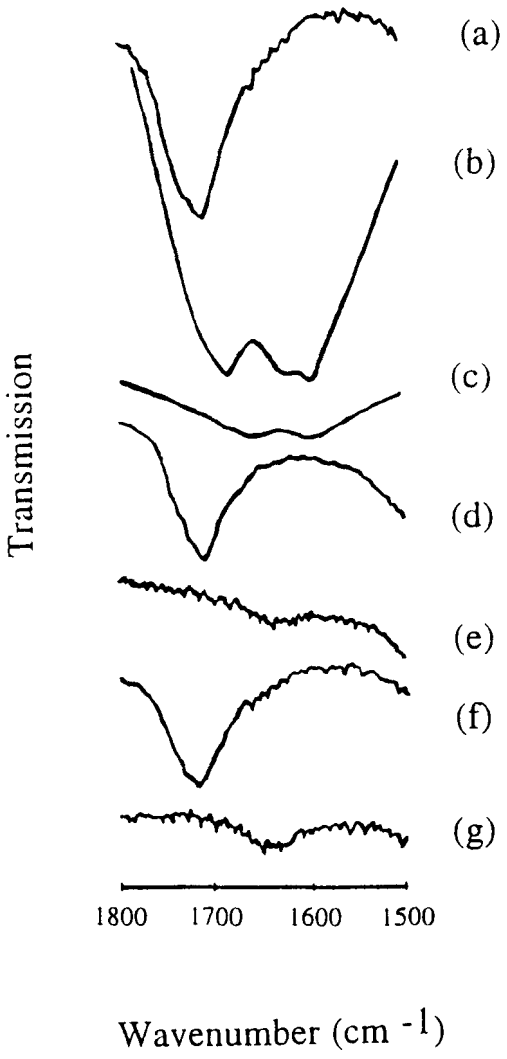

Figure 5. IR spectra of pure UDCA (a), UDCA–urea (1:1) solid dispersion (b), pure urea (c), UDCA–mannitol (1:1) solid dispersion (d), pure mannitol (e), UDCA–PEG 6000 (1:1) solid dispersion (f), and pure PEG 6000 (g).

tol showed carbonyl stretching absorption bands of UDCA at about 1708 cm^{-1}, suggesting that there were no chemical changes or physicochemical interactions in UDCA solid dispersions with mannitol. In the case of UDCA–urea solid dispersion, the broad bands were observed at about 1683 and 1598 cm^{-1}. These bands were considered to be the superimposed bands of the carbonyl stretching bands of UDCA and urea. In the UDCA–PEG 6000 system, the carbonyl stretching band was observed at 1718 cm^{-1}, which is 10 cm^{-1} higher wavenumber than that of the UDCA crystals. This may indicate that hydrogen bonds were formed between the carnonyl oxygen atoms of UDCA and PEG 6000.

Solubility and Dissolution Profiles

The solubility of UDCA in 1:1 ethanol–water mixture at 37°C was found to be 18.6 mg/ml. The effects of carrier concentration on UDCA solubility was studied and the solubility profiles are shown in Fig. 6. A slight increase in the solubility of UDCA was found with an increase of urea and PEG 6000 concentrations. The addition of mannitol did not affect the solubility of UDCA under the test condition.

Dissolution tests were performed for UDCA crystals and UDCA solid dispersions containing PEG 6000, urea, or mannitol in 1:1 weight ratio of drug to carrier. The dissolution profiles are shown in Fig. 7. The solid dispersions demonstrated a significant increase in the dissolution rate of UDCA depending on the type of carrier molecules. The rate of UDCA dissolution from UDCA–urea solid dispersion was the greatest compared to that from UDCA–PEG 6000 and UDCA–mannitol solid dispersions. This result might be due to the improvement of wetting, and the high solubility of UDCA in the mixed solvent of water and ethanol containing urea. In the case of UDCA–mannitol solid dispersion, even the XRD showed no crystalline peak of UDCA; the dissolution of UDCA from UDCA–mannitol solid dispersion was lower than that from UDCA–urea and UDCA–PEG 6000 solid dispersions. This could be due to the low solubility of mannitol in ethanol (8), low solubility of UDCA observed in the solvent used, and the low wettability. The dissolution of UDCA from UDCA–mannitol solid dispersion, however, was much higher than the dissolution of UDCA crystals alone. It has been suggested (13,14) that higher dissolution rate of the dispersed drug from the solid dispersion was a result of drug molecular dispersion formation. This study has demonstrated the amorphous formation of UDCA in solid dispersions with three carriers, PEG 6000, urea, and mannitol. The explanation for enhancement in drug

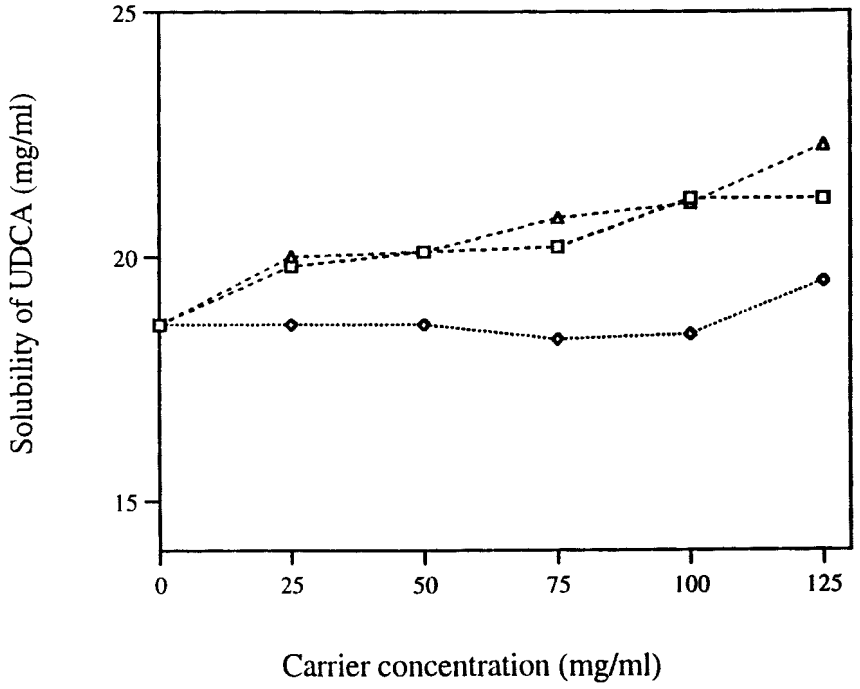

Figure 6. Solubility changes of UDCA in H_2O–Ethanol (1:1) mixture by the addition of urea (□), mannitol (◇), and PEG 6000 (Δ).

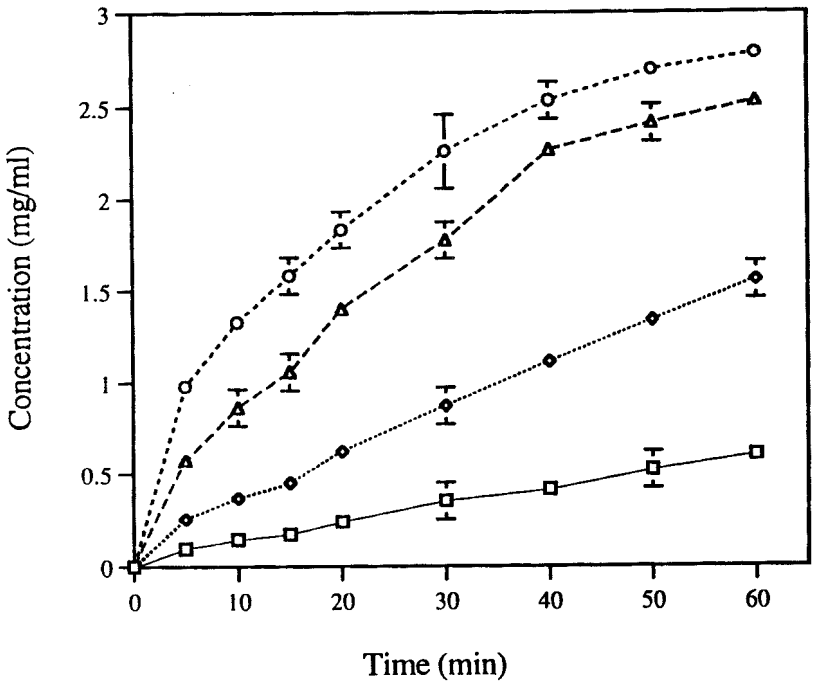

Figure 7. Dissolution profiles of UDCA from pure UDCA (□), UDCA–mannitol solid dispersion (◇), UDCA–urea solid dispersion (○), and UDCA–PEG 6000 solid dispersion (Δ). Bars show the standard deviation.

dissolution rate lies in the specific characteristics of carrier used.

ACKNOWLEDGMENTS

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