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Improved dissolution of ofloxacin via solid dispersion

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Abstract

The objective of this study was to improve the dissolution rate of a sparingly water soluble drug, ofloxacin, by solid dispersion systems with urea and mannitol. Differential scanning calorimetry (DSC), powder x-ray diffraction (PXRD) analysis and infrared spectroscopy (IR) were performed to evaluate the physicochemical properties of the prepared solid dispersions. The dissolution rate of ofloxacin was markedly increased in solid dispersion of urea and mannitol. Solubility studies revealed a marked increase in the solubility of ofloxacin with an increase in urea concentration. Mannitol concentration had no effect on the solubility of ofloxacin. The PXRD study revealed that the crystallinity of ofloxacin was decreased as the ratio of drug to carrier was decreased. The results from DSC and IR indicated that there was no interaction between drug and carriers. © 1997 Elsevier Science B.V.

Keywords: Ofloxacin; Urea; Mannitol; Dissolution rate; Solubility; Solid dispersion

1. Introduction

Ofloxacin (OFX) is a new 4-quinolone derivative with high activity against a wide range of gram-positive and gram-negative bacteria. It is known to exert its antibacterial action by antagonism of the enzyme DNA gyrase (bacterial topoisomerase II), an enzyme that introduces negative supertwists into DNA and separates interlocked DNA molecules. Ofloxacin antagonizes these enzymetic activities, interfering with DNA replication, segregation of bacterial chromosomes, transcription, and other cellular processes and damaging DNA (Gellert, 1981; Wolfson and Hooper, 1989; Sanders, 1992). Unfortunately, ofloxacin has shown pharmaceutical problems of water solubility. Because of its sparing solubility in water, the dissolution of ofloxacin from its dosage form after oral administration which is an important factor related to its bioavailability, is usually the rate-limiting step in the absorption process (Bates et al., 1967; Kitamori and Iga, 1971).

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During the past 30 years, there has been a great deal of interest in using solid dispersions to improve the dissolution rate and the bioavailability of poorly water soluble drugs (Chiou and Riegelman, 1971; Kerc et al., 1993; Jachowicz et al., 1993; Kai et al., 1996; Suzuki et al., 1996). Various water soluble inert materials have shown to improve the dissolution rate and bioavailability of many drugs (Allen et al., 1978; Ghanen et al., 1982; Miralles et al., 1982; Jafari et al., 1988; Law et al., 1992; Simonelli et al., 1994; Yagi et al., 1996).

The present work has been undertaken to develope a solid dispersion of ofloxacin using urea and mannitol in order to improve the dissolution behaviour.

2. Materials and methods

2.1. Materials

Ofloxacin (OFX), melting point range 275–277°C was obtained from Daiichi Seiyaku Co. Ltd. (Japan). Urea and mannitol were purchased from Nacalai Tesque Inc. (Japan). All other chemicals were of analytical grade.

2.2. Preparation of OFX solid dispersions

Different ratios of OFX and urea or mannitol were accurately weighed. The solid dispersions were prepared by solvent method using the 1:1 mixture of ethanol/chloroform as a solvent. The mixture was evaporated under vacuum on a water bath at 45°C. After complete evaporation, the solid mass was further dried in vacuum desiccator for 12 h. The dried solid mass was pulverized with a mortar and pestle and then sieved. The solid dispersions of 60–200 mesh were used in the experiment.

2.3. Powder x-ray diffracttometry (PXRD)

A Rigaku Denki 2027 diffractometer using a scintillation counter was used. The x-ray source was Cu-Kα with a Ni filter (30 kV, 5 mA).

2.4. Differential scanning calorimetry (DSC)

The samples were sealed in the aluminum pan. Each sample weight was about 1.5 mg. The measurements, using a Du Pont 910 differential scanning calorimeter connected to a Du Pont 9900 computer/thermal analyzer, were carried out under nitrogen gas flow of 60 ml/min at a heating rate of 10°C/min. The temperature was calibrated with pure indium, with a melting point of 156.60°C. An empty pan was used as a reference.

2.5. Fourier transformed infrared (FT-IR) spectroscopy

IR spectra were obtained by KBr disk method using a computer mediated FT-IR (Nicolet 5ZDX, USA). KBr disks were prepared with a hydrostatic press at a pressure of 5 t/cm^2 for 5 min.

2.6. Solubility measurement

An excess amount of OFX was placed into a 20-ml L-shaped glass test tube containing various concentration of each carrier in 10 ml water. The content of the suspension was equilibrated by shaking for 24 h at 37°C in a thermostatically controlled water bath. The suspension was then filtered through a 1.2-μm millipore membrane filter and the filtrate was suitable diluted and analyzed spectrophotometrically at a wavelength of 280 nm to measure the amount of dissolved OFX. The average of duplicate measurements was reported. The solubility of OFX in water alone at the same temperature was also determined following the same procedure as above.

2.7. Dissolution studies

The dissolution rate of OFX was determined by the modified USP paddle method at 37°C and a rotating speed of 100 rpm. A 10-mm diameter tablet containing 100 mg of OFX which was compressed at 2 t/cm^2 was placed and fixed at the center of the bottom of a beaker containing 1000 ml of distilled water as medium. The other end of the tablet except the surface was sealed to allow a

constant surface contacted to the medium throughout the dissolution run. A 5-ml portion of the solution was taken out periodically, and the same amount of distilled water at the same temperature was replaced to keep the medium amount constant throughout the test. The sample solution was suitable diluted in the distilled water and the concentration of OFX was determined spectrophotometrically at 280 nm. The measurement was performed in triplicate. The concentration of OFX in each sample was calculated and plotted versus time.

3. Results and discussion

3.1. Crystalline property and thermal behaviour of OFX solid dispersions

The PXRD patterns of OFX solid dispersion are shown in Fig. 1. The physical mixtures of OFX with either urea or mannitol at 1:19 and 1:4 drug to carrier ratios showed both characteristic diffraction peaks of OFX and carrier. In both OFX-urea and OFX-mannitol solid dispersion systems, the intensity of diffraction peaks attributed to OFX gradually decreased with increased carrier content. In the solid dispersion of OFX-urea (1:19), the diffraction peaks of OFX was not observed whereas the diffraction peaks of urea was noted. This indicated that OFX in this solid dispersion system was in amorphous state. At 1:4 ratio, the diffraction peaks due to OFX were of low intensity in comparison with those of intact OFX. It was indicated that the crystallinity of OFX was markedly low in the solid dispersion with urea. In the case of solid dispersion of OFX-mannitol system, the OFX diffraction peaks with low intensity was still observed at 1:19 ratio, indicating that OFX was not in amorphous state as that of 1:19 OFX-urea solid dispersion. For further studies, the solid dispersions of 1:4 ratio were chosen, as a higher drug content is more suitable for practical use.

The DSC thermograms of OFX, urea, mannitol, and OFX solid dispersions with these carriers are shown in Fig. 2. The DSC data of endothermic peaks and ΔH_f are listed in Table 1. The DSC curves of pure OFX, urea and mannitol demonstrated the melting points at 277.5, 136.9 and 168.6°C respectively. The thermograms of OFX-

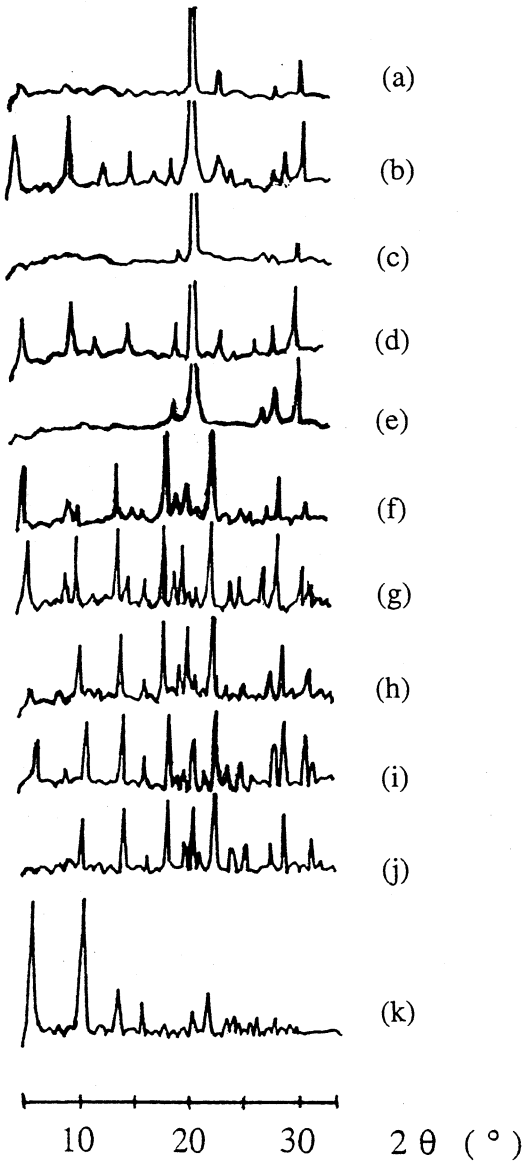

Fig. 1. PXRD patterns of (a) OFX-urea (1:4) solid dispersion, (b) OFX-urea (1:4) physical mixture, (c) OFX-urea (1:19) solid dispersion, (d) OFX-urea (1:19) physical mixture, (e) pure urea, (f) OFX-mannitol (1:4) solid dispersion, (g) OFX-mannitol (1:4) physical mixture, (h) OFX-mannitol (1:19) solid dispersion, (i) OFX-mannitol (1:19) physical mixture, (j) pure mannitol, and (k) pure OFX.

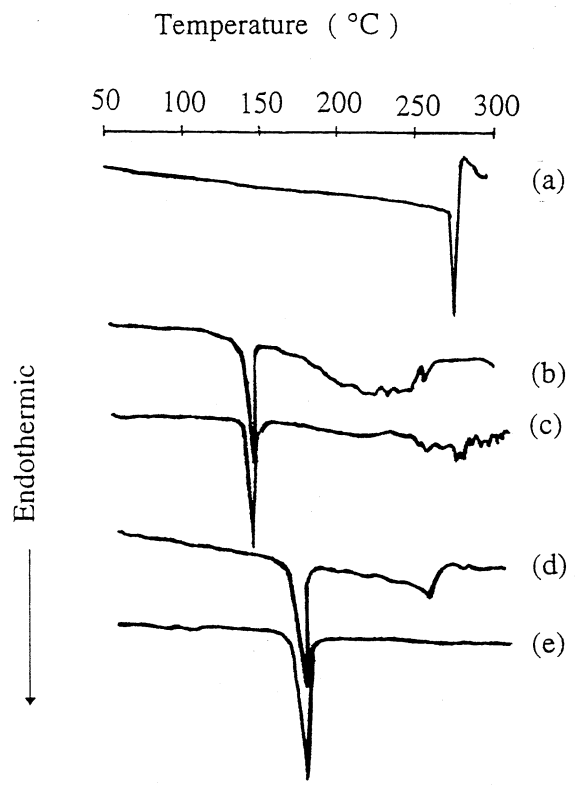

Fig. 2. DSC thermograms of (a) pure OFX, (b) OFX-urea (1:4) solid dispersion, (c) pure urea, (d) OFX-mannitol (1:4) solid dispersion, and (e) pure mannitol.

urea solid dispersions showed a melting peak of urea at 138.6°C and a broad endothermic peak around 200–250°C. It was suggested that a small crystalline portion of OFX existed in this solid dispersion melted at lower than melting point of intact OFX. The melting endotherm could not be

Table 1
Endothermic peaks and ΔH_f of OFX and OFX-solid dispersions

Substances	Endothermic peak (°C)	ΔH_f (J/g)
OFX	277.5	126.7
OFX-urea	138.6	160.8
OFX-mannitol (1:4)	169.8	214.5
	250.6	24.02
Urea	136.9	241.3
Mannitol	168.6	387.1

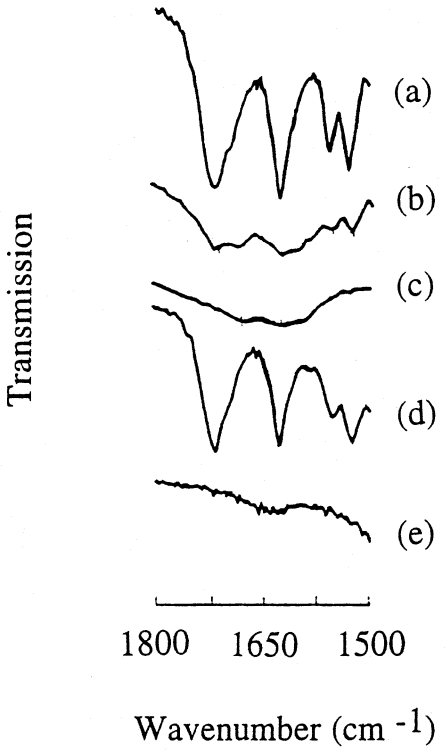

Fig. 3. Expanded IR spectra of (a) pure OFX, (b) OFX-urea (1:4) solid dispersion, (c) pure urea, (d) OFX-mannitol (1:4) solid dispersion, (e) pure mannitol.

clearly observed. In OFX-mannitol solid dispersion, the thermogram showed a melting peak of mannitol at 169.8°C and exhibited a small broad peak at 250°C, which was attributed to the melting of OFX. These DSC results demonstrated that the solid dispersions of both OFX-urea and OFX-mannitol systems were monotectics (Craig, 1990a). It was noticed that the thermal characteristics of a material may be altered when suspended in a melt of the carrier (Craig, 1990b).

The IR spectra of pure OFX, urea, mannitol, and the solid dispersion of OFX-urea and OFX-mannitol are shown in Fig. 3. In the carbonyl frequency region, OFX showed a strong band at 1713 and 1622 cm^{-1} which was attributed to carboxylic C=O stretching and cyclic carbonyl C=O stretching respectively. The solid dispersions

of OFX-mannitol also showed these regions of carbonyl frequency belonging to OFX. On the other hand, the solid dispersion of OFX-urea showed the broad spectra at 1676 and 1625 cm^{-1}, which were the superimposed peaks between OFX and urea.

The above mentioned results suggested that there was no physicochemical interaction between OFX and the two carriers used.

3.2. Solubility and dissolution profiles.

The solubility of OFX in water at 37°C was found to be 2.52 mg/ml. The effect of the addition of urea, and mannitol on the solubility of OFX was studied. The solubility profiles of OFX in the various aqueous concentrations of urea, and mannitol are shown in Fig. 4. Mannitol did not significantly increase the solubility of OFX, whereas the addition of urea provided the increase in OFX solubility. It was suggested that urea might formed the complex with OFX and consequently enhanced the OFX solubility (Shah and Flanagan, 1990; Bloch et al., 1982).

Dissolution of OFX alone and OFX solid dispersions containing urea, and mannitol in the 1:4 ratio of drug to carrier were investigated. The dissolution profiles are shown in Fig. 5. Both of the solid dispersions provided an increase in the dissolution rate of OFX. The enhancement of OFX dissolution from solid dispersions depended on the type of carrier molecules. The dissolution rate of OFX from OFX-urea solid dispersion was significantly higher than that from OFX-mannitol solid dispersion and OFX alone. This result might be due to some of the same factors responsible for solubility enhancement discussed earlier and because of the wetting effect of the highly water soluble urea in intimate contact with OFX. Moreover, it was indicated that the solid dispersion of OFX-urea at this ratio could alter the solid state of drug, thus the dissolution enhancement was observed. This alteration of solid state of OFX was confirmed by the decrease in OFX diffraction peak intensity in PXRD patterns. It has been suggested that the higher dissolution rates of the dispersed drugs from the solid dispersions were a result of the decrease in crystallinity.

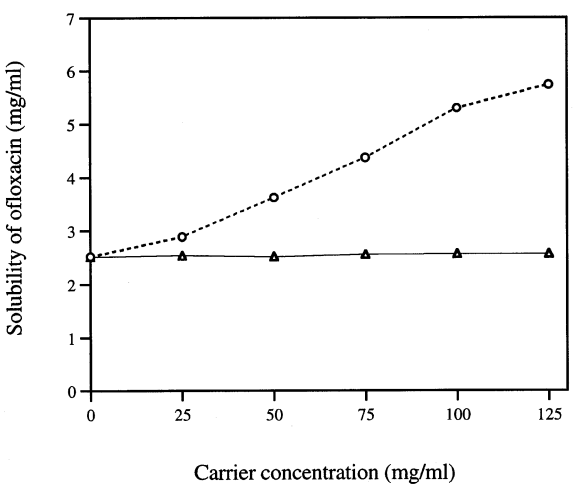

Fig. 4. Solubility profiles of OFX in aqueous solution of urea (○), and mannitol (△).

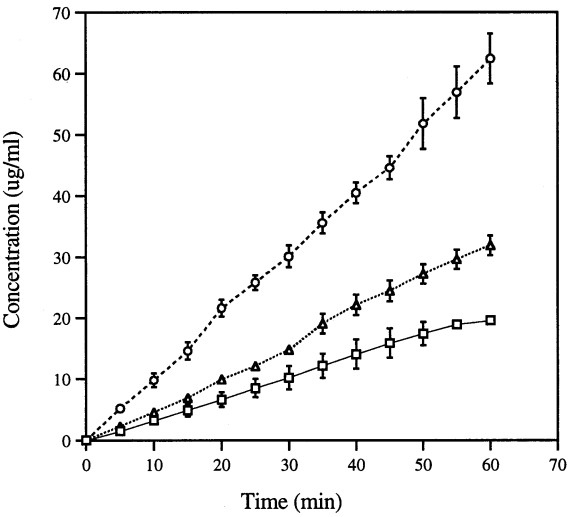

Fig. 5. Dissolution profiles of pure OFX (□), OFX-mannitol (1:4) solid dispersion (△), OFX-urea (1:4) solid dispersion (○). (Bars show S.D.).

As the result of the higher crystallinity of OFX in OFX-mannitol solid dispersion, the dissolution of OFX from OFX-mannitol solid dispersion was lower when compared to OFX-urea solid dispersion. It was demonstrated that the solid dispersion of OFX, a poorly water soluble drug, with two common water soluble carriers, urea and mannitol, could enhance drug dissolution rate. The dif-

ference in dissolution results could be explained by the characterization of solid dispersions by PXRD and thermal analysis. It was concluded that the dissolution of OFX could be improved by the formation of a solid dispersion. The greatest enhancement in OFX dissolution was achieved from OFX-urea solid dispersion.

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