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Solid state properties of pure UC-781 and solid dispersions with polyvinylpyrrolidone (PVP K30)

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Abstract

The purpose of this study was to elucidate the physical structure of solid dispersions of the antiviral agent UC-781 (N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furancarbothioamide) with polyvinylpyrrolidone (PVP K30). Solid dispersions were prepared by co-evaporating UC-781 with PVP K30 from dichloromethane. The physicochemical properties of the dispersions were evaluated in comparison with the physical mixtures by differential scanning calorimetry (DSC), X-ray powder diffraction, and FT-IR spectroscopy. We investigated the single crystal structure of pure UC-781. The data from single crystal analysis showed that UC-781 crystallized with orthorhombic symmetry in the space group *Pcab*. Its cell parameters were found to be; $a = 8.1556(7)$ Å, $b = 17.658(2)$ Å and $c = 23.609(2)$ Å; the unit cell was made up of eight molecules of UC-781. The molecules formed intermolecular hydrogen bonds between NH and thio groups, and were packed in a herringbone-like structure. The data from X-ray powder diffraction showed that crystalline UC-781 was changed into the amorphous state by co-evaporating it with PVP K30. From differential scanning calorimetry analysis, UC-781 peaks were observed in the DSC curves of all physical mixtures, while no peaks corresponding to the drug could be observed in the solid dispersions with the same drug composition up to the concentration of 50% w/w. The data from FT-IR spectroscopy showed the distortions and disappearance of some bands from the drug, while other bands were too broad or significantly less intense compared with the physical mixtures of the crystalline drug in PVP K30. Furthermore, the results from IR spectroscopy demonstrated that UC-781 interacted with PVP K30 in solid dispersions through intermolecular H-bonding.

Introduction

UC-781 (N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furancarbothioamide) is a member of the thiocarboxanilide derivatives. It is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), and is extremely potent as an inhibitor of HIV-1 replication in cell culture (Balzarini et al 1996). Therefore, this compound should be regarded as a potential candidate for the treatment of HIV-1-infected individuals or as a prophylactic agent administered to individuals at risk of an HIV-1 infection (Balzarini et al 1998). A major problem in the development of an oral solid dosage form of UC-781 is its extremely poor aqueous solubility. As a consequence, its oral bioavailability may be limited and/or variable due to dissolution-limited oral absorption. Previous studies in our laboratory have shown that UC-781 easily crosses Caco-2 monolayers under

optimized experimental conditions, therefore, no permeability-limited absorption is expected (Augustijns et al 2000).

Solid (molecular) dispersions of drugs in water-soluble carriers (polymers) have been proposed frequently in literature as a strategy to improve the dissolution rate and bioavailability of poorly soluble drugs (Stupak & Bates 1972, 1973). We have recently formulated and characterized solid dispersions of UC-781 with PEG 6000 and Gelucire 44/14 (Damian et al 2000). Its dissolution rate was improved which is possibly advantageous with respect to its bioavailability issue. However, it was shown that with these carriers the crystalline nature of UC-781 was maintained. The drug was not transformed into the amorphous state by using PEG 6000 and Gelucire 44/14 as carriers.

Several other carriers to improve the dissolution of insoluble drugs have been discussed in the literature (Ford 1986), including polyvinylpyrrolidone (PVP K30). It is a synthetic water-soluble linear polymer used in a large number of pharmaceutical formulations and it is able to dissolve in a variety of organic solvents as well. The objective of this study was to elucidate the physical structure of solid dispersions of UC-781 with PVP K30 using differential scanning calorimetry, powder X-ray diffraction, and FT-infrared spectroscopy. Preliminary experiments performed in our laboratory showed that the dissolution rate of UC-781 was significantly improved when co-evaporated with PVP K30 compared with the physical mixtures of the drug and the carrier. However, at that time, the exact nature of the drug in the carrier was not investigated. In this study, we have investigated the single crystal structure of pure UC-781, and we have used the data obtained to elucidate the mode of interaction of UC-781 when combined with PVP K30.

Materials and Methods

Materials

UC-781 was kindly supplied by Uniroyal Chemical Company Inc. (Middlebury, CT, and Guelph, Ontario, Canada). KBr (IR-grade) was obtained from Acros Organics (Geel, Belgium). PVP K30 (Kollidon) was provided by BASF (Ludwigshafen, Germany). All other materials used were of analytical or HPLC grade.

Crystal preparation, mounting and data treatment

X-ray single crystals were obtained by slow evaporation (two to three days) from methanol at room temperature. UC-781 crystallized in clusters of very fine needle-like crystals. Crystal structure determination was carried out following the general procedures as described by Stout & Jensen (1989) in X-ray structure determination. The crystals were measured at 293 K on a Siemens P4 four-circle diffractometer with graphite monochromatized CuKα radiation ($\lambda = 1.54184$ Å). Unit-cell dimensions were obtained from a least-squares refinement using the setting angles of 53 centred reflections in the range of $10 \leqslant 2\theta \leqslant 63°$. Three reflections were selected and used as intensity standards to monitor the measurements at 1-h intervals. The intensity of the standard peaks varied by 10% during data collection. The intensity data were corrected for Lorentz-polarization, linear decay (Siemens (1996): XSCANS X-ray Single Crystal Analysis Software, Version 2.2. Siemens Analytical X-ray Instruments Inc., Madison, WI), and for absorption (Siemens (1989): XEMP Empirical Absorption Correction Program. Siemens Analytical X-ray Instruments Inc., Madison, WI), the latter using Ψ-scans. The structure was resolved by direct methods using SIR92 (Altomare et al 1993) and refined on F^2 using a full-matrix least-squares technique with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were included in calculated positions and refined as riding, with U_{iso} (isotropic displacement parameter) values 1.3-times the U_{eq} (equivalent isotropic displacement parameter) of the parent atom. A secondary-extinction correction was applied and the extinction coefficient was refined. In the last stage of refinement, no parameter varied more than 0.001 of its standard deviation. The final difference Fourier spectrum had no interpretable peaks. Molecular graphics were produced using DIAMOND (DIAMOND-Visual Crystal Structure Information System, G. Bergerhoff, Gerhard-Domagk-Str. 1, 53121 Bonn, Germany). PARST (Nardelli 1983, 1995) and PLATON (Spek 1998) were used for analysis of geometry. Other experimental conditions for data measurement and refinement are summarized in Table 1.

Preparation of solid dispersions and physical mixtures

Solid dispersions were prepared using the solvent evaporation method. Dispersions containing 2 to 70% w/w of UC-781 were prepared by dissolving a total of 400 mg drug and PVP K30 in 20 mL dichloromethane. The solvent was then removed rapidly by evaporation in a rotary evaporator under reduced pressure at 323 K. The resulting solid dispersions were dried further at 323 K for one week under vacuum. The dispersions were

Table 1 Crystal data and structure refinement of UC-781.

Empirical formula	$C_{17}H_{18}ClNO_2S$
Formula weight	335.83
Temperature	293(2)
Wavelength	1.54184 Å
Crystal habit	Needle
Crystal system, space group	Orthorhombic, *Pcab*
Unit cell dimensions	$a = 8.1556(7)$ Å, $b = 17.658(2)$ Å, $c = 23.609(2)$ Å, $\alpha = \beta = \gamma = 90°$
Volume	3399.9(6) Å^3
Z	8
Calculated density	1.312 Mg m^{-3}
Absorption coefficient	3.184 mm^{-1}
F(000)	1408
Crystal size	$0.4 \times 0.08 \times 0.06$ mm
θ range for data collection	3.74 to 69.23°
Index ranges	$-1 \leqslant h \leqslant 8$; $-1 \leqslant k \leqslant 21$; $-1 \leqslant l \leqslant 28$
Reflections collected/unique	3842/2980 ($R_{int} = 0.0386$)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2980/0/203
Goodness-of-fit on F^2	1.032
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0465$, $wR_2 = 0.1203$
R indices (all data)	$R_1 = 0.071$, $wR_2 = 0.1451$
Extinction coefficient	0.00154(17)
Largest difference peak and hole	0.315 and −0.241 Å^{-3}

pulverized, passed through a 350-μm screen and then stored in a desiccator (0% r.h.) at room temperature until use. Physical mixtures were prepared by triturating UC-781 and PVP K30 for 3 min in a mortar until a homogenous mixture was obtained. Physical mixtures ranging from 2 to 50% (w/w) UC-781 were prepared, and then treated in the same way as solid dispersions.

Thermal analysis

Differential scanning calorimetry (DSC) measurements were carried out using a Perkin-Elmer DSC-7 differential scanning calorimeter (Perkin-Elmer, Norwalk, CT) equipped with a liquid nitrogen subambient accessory (Perkin-Elmer, Norwalk, CT). The instrument was operated under nitrogen purge gas at a rate of 20 mL min^{-1}. Samples (1–6 mg) were weighed into hermetically sealed aluminium pans (TA Instruments, Brussels, Belgium) and heated at a scanning rate of 5 K min^{-1}. The temperature calibration was performed with indium and water as standards, while heat flow was calibrated using indium. Data obtained were treated mathematically using the Pyris Software 3.6 (Perkin-Elmer, Norwalk, CT). For the measurement of glass transition temperature (T_g) of pure drug, UC-781 was first heated from 373 K to 413 K at 5 K min^{-1}, and then quench-cooled to 243 K. The sample was then rescanned at 5 K min^{-1} from 243 K to 413 K, and T_g was taken as the midpoint at which the two tangents intersected the measurement curve.

X-ray powder diffraction

X-ray powder diffraction patterns were obtained from an automated Philips PW 1050/25 powder X-ray diffractometer using Ni-filtered and CuKα radiation (λ = 1.54178 Å). Powder samples of solid dispersions and physical mixtures were filled in a cup holder with a glass on the lower part to allow X-rays to pass through. The X-ray patterns were collected with 45 kV of tube voltage and current of 18 mA in the angular range of $4° < 2\theta < 75°$ in a step scan mode (step width 0.02°, counting time 2 s/step).

FT-infrared spectroscopy

Two analytical procedures were employed in the characterization of solid dispersions by infrared spectroscopy. In the first part, the data were obtained by using a Perkin Elmer 2000 FT-IR system (Perkin-Elmer, Norwalk, CT) using the KBr disk technique (0.1–1% w/w UC-781 in KBr). KBr tablets were obtained at a pressure of 10 tons. Twelve scans were obtained at a resolution of 2 cm^{-1}. The scanning range was 400–4000 cm^{-1}.

The data in the second part were recorded in KBr using a Brucker IFS 113v FT spectrophotometer, equipped with a Ge/KBr beam splitter and a MCT detector cooled with liquid nitrogen. A total of 100 scans were recorded with a resolution of 1 cm^{-1}. Low temperature measurements were carried out with a liquid nitrogen cryostat. Before recording the spectra, the samples were equilibrated at the desired temperature for 30 min.

Density measurements

The densities of pure UC-781 and PVP K30 were determined using an Air comparison pycnometer (Beckman Model 30, Beckman Instruments, Inc., USA), and were found to be 1.216 and 1.162 g cm^{-3}, respectively. The density of crystalline UC-781 was reduced by 5% so as to have an estimate value of that of the amorphous drug.

Thermogravimetric analysis

To determine the amount of residual water present in the solid dispersions, thermogravimetric analysis was performed using a TGA-50 Thermogravimetric An-

alyser (Shimadzu, Japan). Samples of 8–12 mg were heated in a platinum crucible at a rate of 2 K min^{-1} under reduced pressure, and the loss in weight was recorded.

Results and Discussion

Single crystal results

Figure 1 shows the packing of UC-781 molecules within the unit cell. The purpose of this experiment was to identify the presence of interactions between UC-781 molecules. Two short intramolecular contacts were found at: Cl … O (side chain oxygen) (2.869(2) Å), and S … H (hydrogen atom at position 2 of the phenyl ring) (2.74 Å). The thio-amidic nitrogen was found to form an intermolecular hydrogen bond with a sulphur atom of a neighbouring molecule at a position (1/2 + x, 1/2 − y, z). The hydrogen bond geometry can be described by D-H (N-H: 0.8600 Å), H … A (N-H … S: 2.658 Å), D … A (N … S: 3.480(3) Å) and D-H … A (N-H … S: 160.4 Å), where D represents a donor and A an acceptor of electrons. This hydrogen bond is responsible for packing of molecules in chains along [100]. Packing in the other direction results from interactions of the slightly positively charged hydrogen atoms of methyl groups in the side chain with the electron-rich π-electrons of an aromatic ring system, resulting in a so-called herringbone structure (Figure 1). Other ring interactions were observed between the furan ring and two side chain methyl hydrogen atoms at distances of 3.47 Å each, and between the benzene ring and thio-amidic hydrogen atom and hydrogen atom at position 1 in the side chain at distances 3.48 Å and 3.65 Å, respectively. With respect to this study, the information on hydrogen bonding between neighbouring molecules of UC-781 was crucial, and it will be used to give an idea of the presence of an interaction between UC-781 with PVP K30 in the later sections.

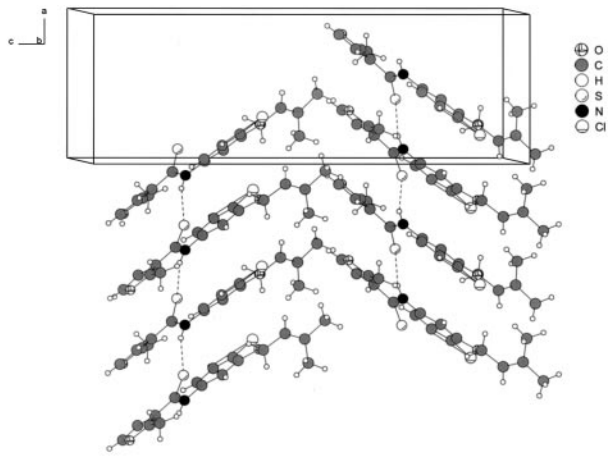

Figure 1 Packing of UC-781 molecules within the unit cell. Dashed lines indicate the intermolecular hydrogen bonding.

Differential scanning calorimetry

Figure 2 shows the DSC curves of UC-781 with PVP K30 in solid dispersions in comparison with the physical mixtures at the same weight ratio. The DSC curve of pure crystalline UC-781 showed a characteristic sharp endothermic peak of the drug at 403.7 K corresponding to its melting point. Physical mixtures of crystalline UC-781 with PVP K30 showed broad melting peaks of the drug, and were shifted toward lower temperatures compared with the pure drug. Other research groups (Iwata & Ueda 1996) have observed the same effect of PVP K30, reducing the melting points of drugs in physical mixtures. Even though no explanation was given for that observation, it seems that in this case PVP K30 was

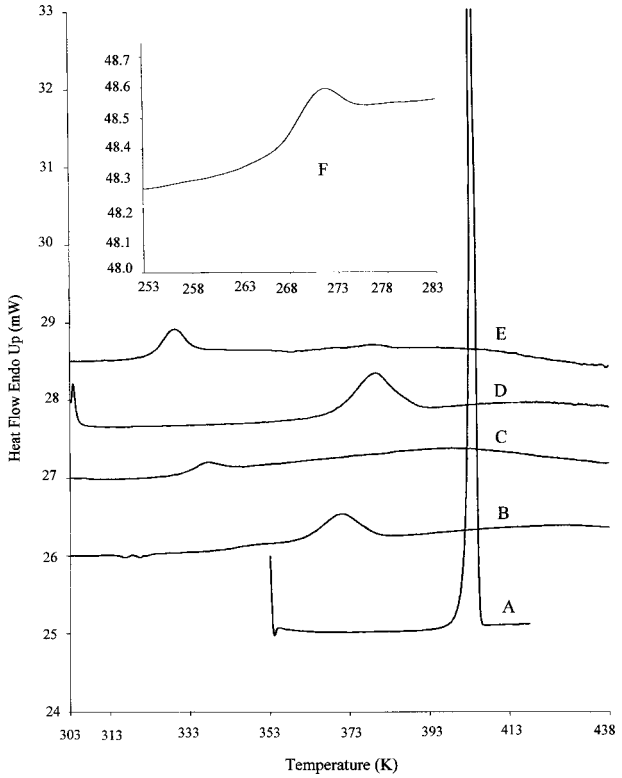

Figure 2 Differential scanning calorimetry curves of UC-781, physical mixtures and solid dispersions of UC-781 in PVP K30 at a scanning rate of 5 K min^{-1}. A, UC-781; B, 20% UC-781 physical mixture; C, 20% UC-781 solid dispersion; D, 50% UC-781 physical mixture; E, 50% UC-781 solid dispersions; F, T_g region of pure UC-781.

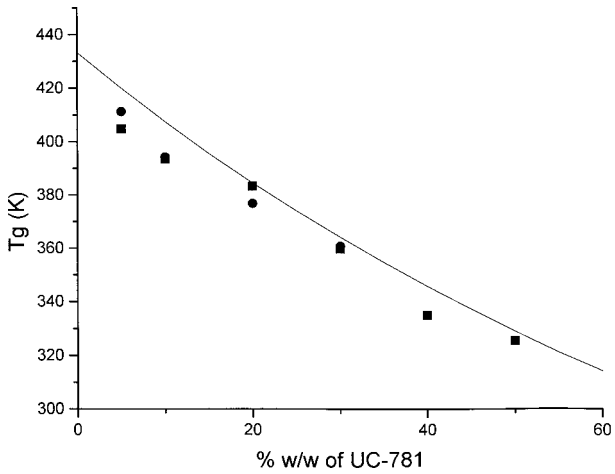

Figure 3 Variation of the T_g of solid dispersions of UC-781 with PVP K30 as a function of % w/w UC-781. The solid line represents theoretical values according to the Gordon-Taylor equation for binary mixtures. ■, Experimental values; ●, theoretical values according to the Gordon-Taylor equation for ternary mixtures. n = 3, RSD $\leqslant 4\%$.

acting as an impurity to UC-781. Solid dispersions did not show the melting peak of the drug up to the concentration of 50% w/w. The absence of melting peaks of UC-781 in the solid dispersions is the result of transformation of the crystalline UC-781 into the amorphous state. PVP K30 is an amorphous polymer, therefore it did not show a melting peak; only its glass transition temperature was noted at 433.3 K. Furthermore, the appearance of a single T_g in the solid dispersions indicated that UC-781 was molecularly dispersed throughout the polymer. The T_g of UC-781 was increased from 266 K to more than 373 K at a low drug concentration in the polymer; even at a high drug concentration (50%, w/w) the T_g value was still high (325 K). The elevation of UC-781 glass transition temperature in the solid dispersions has an advantage with respect to the stability of amorphous systems of drugs (Yoshioka et al 1995).

It is necessary to point out that, due to the fact that the T_g of UC-781 was very low, the amorphous state of pure drug could not be obtained at room temperature. Therefore, it was not possible to compare physical mixtures of amorphous drug and polymer with solid dispersions of drug and polymer.

To study the miscibility between UC-781 and PVP K30, the glass transition temperatures of solid dispersions were plotted against the weight composition of both components. The Gordon-Taylor (G-T) equation was then used to predict the T_g of the solid dispersions by assuming that the two components were miscible at T_g and the free volumes were additive (Gordon & Taylor 1952):

$$T_{gx} = (w_1 T_{g1} + K w_2 T_{g2})/(w_1 + K w_2) \quad (1)$$

where w_1 and w_2 are the weight fractions of UC-781 and PVP K30, respectively. T_{gx}, T_{g1} and T_{g2} are the glass transition temperatures of solid dispersions, UC-781 and PVP K30, respectively. K is a constant defined by the following equation:

$$K \approx (T_{g1}\rho_1)/(T_{g2}\rho_2) \quad (2)$$

where ρ_1 and ρ_2 are the densities of UC-781 and PVP K30, respectively. The glass transition temperature of pure UC-781 and pure PVP K30 were found to be 266 and 433.3 K, respectively. Under normal circumstances, the T_g of the solid dispersions varies between the T_g of pure components and therefore co-evaporating UC-781 with PVP K30 should raise the T_g of the drug. Figure 3 shows the variation of T_g of the solid dispersions as a function of weight composition. The data obtained experimentally (square symbols) showed a slight deviation from the theoretical values (solid line) as predicted by the Gordon-Taylor equation (eqn 1). However, from thermogravimetric analysis it was found that a small amount of water was still present in the samples despite drying for a long time. The water content after drying ranged from 0.25 to 1.5% w/w. The water present will act as plasticizer and will reduce the T_g. Therefore, the theoretical T_g values were then recalculated by using a modified form of the G-T equation (Taylor & Zografi 1998) (eqn 3):

$$T_{gx} = \frac{(w_1 T_{g1} + K_1 w_2 T_{g2} + K_2 w_3 T_{g3})}{(w_1 + K_1 w_2 + K_2 w_3)} \quad (3)$$

where w_1, w_2, and w_3 are the weight fractions of water, UC-781 and PVP K30, respectively, and T_{g1}, T_{g2} and T_{g3} are their corresponding glass transition temperatures. T_{gx},K_1 and K_2 have the same meaning as in equation 1. The T_g value of water used in the calculation was 138 K. The recalculated values are plotted as circles (Figure 3). The values were close to those obtained experimentally but slightly lower compared with those obtained by using equation 1. The similarity of these data suggests the absence of strong interactions between UC-781 and PVP K30. However, the possibility of hydrogen bonding between these two components will be clarified further by the data obtained from IR-spectroscopy.

X-ray powder diffraction

To elucidate further the amorphous state of UC-781 in solid dispersions observed by DSC analysis, the dis-

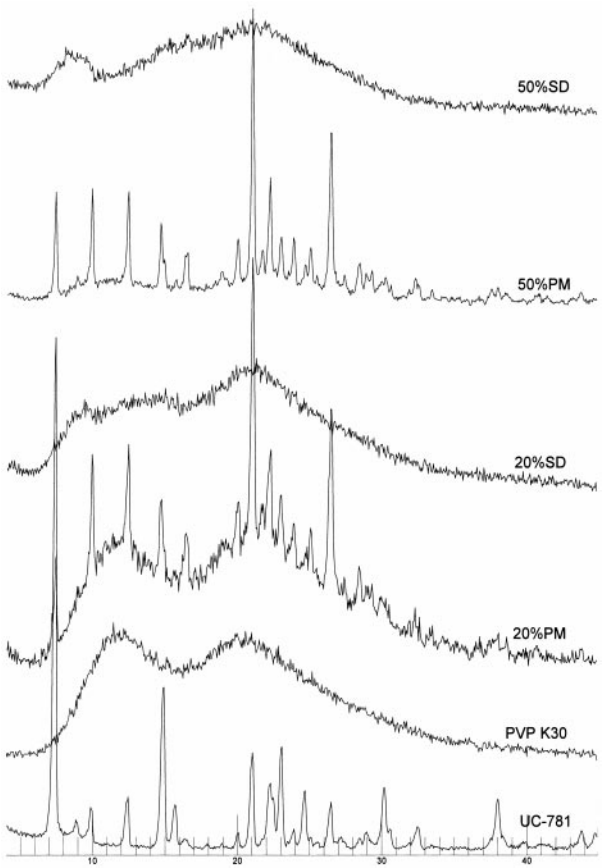

Figure 4 X-ray powder diffraction patterns of solid dispersions (SD) and physical mixtures (PM) of UC-781 with PVP K30. The percentages represent UC-781 in the dispersions.

persions were analysed by X-ray powder diffraction. The data obtained are presented in Figure 4. The diffraction spectrum of pure UC-781 showed that the drug was crystalline in nature as demonstrated by the sharp and numerous peaks in its spectrum. From our data, it was clear that UC-781 was in the amorphous state in the solid dispersions up to the concentration of 50% w/w. These results corresponded well with those obtained from DSC analysis. The loss of UC-781 peaks in solid dispersions indicated a change in its crystal structure or modification of its unit cell. At a concentration of 70% w/w drug in solid dispersions, all features of crystalline UC-781 reappeared showing that PVP K30 was not able to prevent crystallization of UC-781 at higher concentrations of the drug (data not shown). In physical mixtures of crystalline UC-781 and PVP K30, the drug was detected even at a concentration of 5% w/w; upon increasing the concentration of the drug, the peaks from UC-781 became more intense and comparable with that of pure drug. From this section, it was clear that PVP K30 was able to inhibit the crystallization of UC-781 on removal of the solvent. This was probably by forming intermolecular hydrogen bonding or as a result of higher viscosity of PVP K30 acting as a physical barrier for molecular diffusion of UC-781 in the carrier.

FT-IR spectroscopy

To investigate the possibility of interaction between UC-781 and PVP K30 in the solid state, to localise the site of interaction, more information was gathered from IR spectroscopy. From the structures of UC-781 and PVP K30 it could be assumed that the possible interaction would take place between NH of UC-781 and the carbonyl group of PVP K30. Any sign of interaction would therefore be reflected by shifts of N-H or C═O vibrations. The evidence of intermolecular hydrogen bonding mentioned in the single crystal results section was confirmed by scanning a sample of pure UC-781 at room temperature, 213 K, and 77 K. The data obtained (Figure 5) showed that the characteristic NH stretch of UC-781 shifted to a lower wavenumber (i.e. from 3208

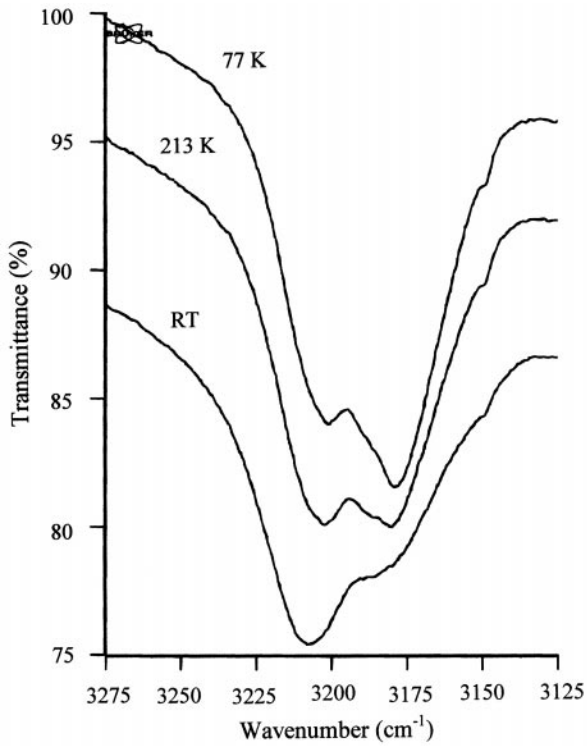

Figure 5 IR spectra of pure UC-781 showing the effect of intermolecular hydrogen bonding of UC-781 molecules on the N-H vibrations as a function of temperature. RT, room temperature

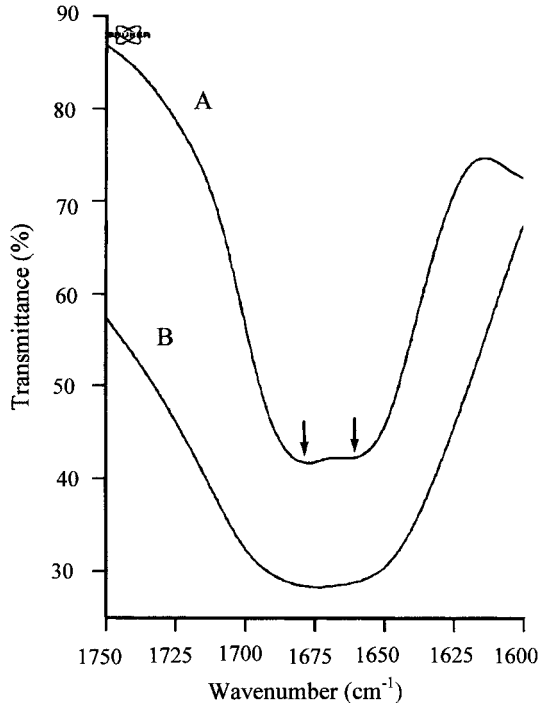

Figure 6 IR carbonyl stretching region of the solid dispersions of UC-781 with PVP K30 (A) and pure PVP K30 (B).

to 3179 cm^{-1} at room temperature and 77 K, respectively) at lower temperature. This was evidence for intermolecular hydrogen bonding between UC-781 molecules, since at lower temperature the intermolecular distances are shorter due to the contractions of the crystals. This shorter distance results in stronger hydrogen bonds. This effect was accompanied by an increase in frequency of C-N stretch and NH deformation at the same conditions. These findings indicated that pure UC-781 did not exist as an isolated molecule in the solid state. With respect to the solid dispersions, it was interesting to note that the incorporation of UC-781 into PVP K30 in solid dispersions did modify its peak intensities and shape. Also, a shift of NH group of UC-781 was observed in solid dispersions. Since it was not possible to obtain pure amorphous UC-781 at room temperature, it was not clear if this shift was due to amorphous drug in solid dispersions or due to interaction with PVP K30. Opposite to the situation in the pure polymer, the carbonyl stretching region of PVP K30 in the solid dispersions showed two peaks (Figure 6) at 1678 and 1663 cm^{-1}. The peak at the higher wavenumber could be assigned to the carbonyl group of PVP K30 H-bonded with water while the one at the lower wavenumber was the result of the carbonyl group of PVP K30 H-bonded with the NH group of UC-781. The H-bonding of the carbonyl group of PVP K30 with water was weak compared with the NH group of UC-781, because the group electron contribution in the latter was stronger. Therefore, these two types of interactions were reflected by the appearance of two peaks in the carbonyl region of solid dispersions and this proved the existence of interactions between UC-781 and PVP K30. In addition, the νCN in the solid dispersions was affected by this interaction, although this could also be partially due to the consequence of the amorphous state of UC-781 in the dispersions. The interaction between UC-781 and PVP K30 could act also as an additional physical barrier to the molecular movement of UC-781, thus suppressing the formation and growth of a lattice within the dispersions.

Conclusions

The data obtained from DSC and X-ray powder diffraction experiments showed that PVP K30 was able to inhibit crystallization of UC-781 in solid dispersions. The presence of interaction between UC-781 and PVP K30 could probably be reflected by the appearance of two populations of peaks in the carbonyl region of PVP K30. The crystallization inhibition of the amorphous state of UC-781 in solid dispersions could be explained as a result of elevation of T_g of the drug, the interaction between the drug and the carrier or as a result of high viscosity of the carrier, which may then act as a barrier in preventing the crystallization of UC-781. From the results of this study, it was apparent that the amorphous form of the drug was responsible for the enhanced dissolution of UC-781 observed in our previous studies. Furthermore, the findings of this study indicated that the transformation of insoluble drugs into the amorphous state might be a useful strategy in improving their dissolution properties.

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