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Physical stability of solid dispersions of the antiviral agent UC-781 with PEG 6000, Gelucire® 44/14 and PVP K30

F. Damian [a], N. Blaton [b], R. Kinget [a], G. Van den Mooter [a,*]

[a] *Laboratorium voor Farmacotechnologie en Biofarmacie, K.U. Leuven, Campus Gasthuisberg O+N, B-3000 Leuven, Belgium*
[b] *Laboratorium voor Analytische Chemie en Medicinale Fysico-Chemie, K.U. Leuven, B-3000 Leuven, Belgium*

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Abstract

This paper describes the physical stability of solid dispersions of UC-781 with PEG 6000, Gelucire® 44/14 and PVP K30 prepared by the solvent and melting methods. The concentration of the drug in the solid dispersions ranged from 5 to 80% w/w. The solid dispersions were stored at 4–8 and 25 °C (25% RH), then their physicochemical properties were analysed by differential scanning calorimetry (DSC), X-ray powder diffraction and dissolution studies as a function of storage time. The DSC curves of solid dispersions of UC-781 with PVP K30 did not show any melting peaks corresponding to UC-781 after storage, indicating no recrystallization of the drug. The DSC data obtained from PEG 6000 and Gelucire® 44/14 showed some variations in melting peak temperatures and enthalpy of fusion of the carriers. It was shown that the enthalpy of fusion of PEG 6000 in the dispersions increased after storage; it was more pronounced for samples stored at 25 °C compared to those at 4–8 °C indicating the reorganization of the crystalline domains of the polymer. Similarly, the enthalpy of fusion of Gelucire® 44/14 in the solid dispersions increased as a function of time. Dissolution of UC-781 from all solid dispersions decreased as a function of storage time. While these observations concurred with the DSC data for all solid dispersions, they were not reflected by X-ray powder diffraction data. It was concluded that it is the change of the physical state of the carriers and not that of the drug, which is responsible for the decreased dissolution properties of the solid dispersions investigated.

Keywords: UC-781; Solid dispersions; Amorphous drugs; PEG 6000; Gelucire 44/14; PVP K30; Stability studies; Non-nucleoside reverse trancriptase inhibitors

1. Introduction

The thiocarboxanilide UC-781 (Fig. 1) is a non-nucleoside reverse transcriptase inhibitor (NNRTIs) that is very potent against HIV-1 in cell culture (Balzarini et al., 1996). Unlike several NNRTIs, UC-781 has been shown not to be markedly affected by single point mutations and

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* Corresponding author. Tel.: +32-16-345-830; fax: +32-16-345-996
E-mail address: guy.vandenmooter@farm.kuleuven.ac.be (G. Van den Mooter).

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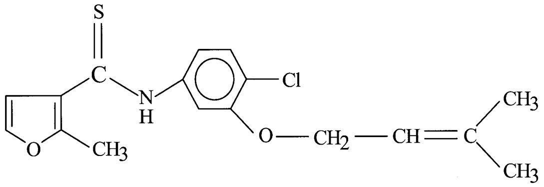


Fig. 1. Chemical structure of UC-781.

it can exert its antiviral activity in nanomolar drug concentration ranges. Therefore, it should be regarded as a potential candidate for the treatment of HIV-1 infected individuals. In particular, UC-781 is currently pursued as a clinical candidate drug for virucidal use. In previous studies (Damian et al., 2001a,b), we described the preparation and characterization of solid dispersions of this poorly water-soluble drug with PEG 6000, Gelucire® 44/14 and PVP K30 as hydrophilic carriers. The solid dispersions were shown to have improved dissolution properties and it was confirmed that UC-781 formed a molecular dispersion when formulated with PVP K30.

The formation of solid dispersions often leads to the conversion of a crystalline drug into a higher energy state, e.g. the amorphous state. Thermodynamically, this high-energy state is metastable and can, in the course of time, be reconverted into the stable crystalline state (Yoshioka et al., 1995; Fukuoka et al., 1986; Izutsu et al., 1994). As a consequence, the biopharmaceutical performance will be affected. Amorphous materials are often highly reactive and unstable to mechanical and thermal stress above their T_g, which may result in significant variation in key physicochemical properties (Hancock and Zografi, 1997). For example, exposure of metastable systems to high humidity may induce changes resulting in a decrease of their dissolution properties. Solid dispersions tend to absorb a higher amount of moisture as compared to physical mixtures of similar composition and this may lead to the induction of crystallization (Takeuchi et al., 2000). Therefore, the present study was undertaken to evaluate the physical stability of solid dispersions of UC-781 with PVP K30, PEG 6000 and Gelucire 44/14. In order to monitor the physical stability of the dispersions, the representative samples of selected batches were stored at two different conditions and their performances were evaluated as a function of time. Dissolution testing and solid state analysis (DSC and X-ray powder diffraction) were carried out at 0, 2, 6, and 12 months.

2. Materials and methods

2.1. Materials

UC-781 was provided by Uniroyal (Middlebury, CT, and Guelph, Ontario, Canada), polyethylene glycol (PEG 6000) and polyvinylpyrrolidone (PVP K30) were provided by BASF (Ludwigshafen, Germany); the melting point of PEG 6000 varies from 56 to 63 °C (The Merck Index-Eleventh edition, 1989). Gelucire® 44/14 was provided by Gattefossé (St. Priest, France); it has a nominal melting point of approximately 44 °C. The actual melting points for UC-781, PEG 6000 and Gelucire® 44/14 used in this study were 130.8, 62.4 and 44.5 °C, respectively (Damian et al., 2001b). Polysorbate 80 was purchased from Ludeco (Brussels, Belgium). All other materials used were of analytical or HPLC grade.

2.2. Methodology

2.2.1. Preparation of solid dispersions

Solid dispersions (SDs) of UC-781 with PVP K30 containing 5–70% w/w of the drug were prepared as follows: To a solution of UC-781 in dichloromethane, the appropriate amount of PVP K30 was added. Next, the solvent was evaporated under reduced pressure at 50 °C and the residues dried for 1 week at 50 °C. The resulting products were subsequently stored in a dessicator for further experiments. Solid dispersions of UC-781 with PEG 6000 and Gelucire® 44/14 were prepared by the melting method. PEG 6000 and Gelucire® 44/14 were melted at 70 and 65 °C, respectively, and mixed with UC-781 until a homogeneous mixture was obtained. The melts were then quench cooled in a freezing mixture of acetone and dry ice. Solid dispersions containing 5–80% of the drug were prepared by this method.

2.2.2. Storage conditions

In order to study the stability of the solid dispersions, the representative samples were placed in airtight containers and stored at 4–8 °C (refrigerator), or in a controlled temperature cabinet at 25 °C (25% RH). The physicochemical properties of these dispersions were evaluated after 0, 2, 6 and 12 months.

2.2.3. Thermal analysis

Differential scanning calorimetry measurements were carried out using a Perkin-Elmer DSC-7 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. Temperature calibration was performed using indium and water as standards, while the heat flow calibrated using indium. Samples (1–10 mg) were weighed in aluminium pans (TA Instruments, Gent, Belgium) and heated at a scanning rate of 3 (Gelucire® preparations) or 5 (PEG 6000 preparations and PVP K30) °C/min, over the temperature interval ranging from 10 to 165 °C.

2.2.4. X-ray powder diffraction

Diffraction patterns were obtained on a Philips PW 1050/80 diffractometer (Philips, Eindhoven, The Netherlands) modified for step-scan operations. Ni-filtered CuKα ($\lambda = 1.54178$ Å) radiation was produced with a Philips PW 1130/00 X-ray generator. Powder samples of solid dispersions were top loaded in a Philips PW 1066 (15×20 mm) flat sample holder. The patterns were collected with a voltage of 45 kV and a current of 32 mA in the angular range of $4^\circ < 2\theta < 75^\circ$ in a step scan mode (step width 0.02°, counting time 2 s/step) using the Philips PW 1710 microprocessor based control and measuring system.

2.2.5. Dissolution studies

The dissolution test was performed according to USP XXIV paddle method (50 rpm). Samples of solid dispersions as powders (≤ 355 μm) ranging from 5 to 20% w/w of UC-781 were added to the dissolution medium (1000 ml of 0.2% (w/v) polysorbate 80 in milliQ water). The temperature of the dissolution medium was maintained at 37 ± 0.1 °C. Samples of 2 ml were withdrawn at various time intervals and the amount taken was immediately replaced with fresh dissolution medium maintained at the same temperature. The corresponding concentrations of UC-781 were determined by HPLC using a calibration curve.

2.2.6. Analysis of UC-781

Concentrations of UC-781 were determined using an isocratic HPLC method. The HPLC system consisted of a LiChroGraph® L-7100 HPLC pump, an autosampler model L-7200 equipped with a 100 μl loop, a UV detector model L-7400 set at 297 nm, and an Interface D-7000, all from Merck-Hitachi (Darmstadt, Germany). UV signals were monitored and peaks were integrated using the D-7000 HSM software. All chromatographic separations were performed at room temperature. The 25.0×0.5 cm column was packed with LiChrospher® 100 RP-18 (5 μm) (Merck, Darmstadt, Germany). The mobile phase consisted of acetonitrile:water (90:10, v/v) and was filtered through a membrane filter (0.45 μm) and degassed by ultrasonication before use. The flow rate was 1 ml/min. The quantification and detection limits of UC-781 were 0.15 and 0.075 μmol/l, respectively.

3. Results and discussion

3.1. Differential scanning calorimetry

Representative DSC curves of solid dispersions of UC-781 with PEG 6000 after one year of storage are shown in Fig. 2(a). The main observation that can be made from these curves is that the melting behaviour of PEG 6000 changed as a function of time. Broadening of the melting peaks was observed while some samples showed shoulders on the leading edge of the melting peak indicating that folding of PEG chains occurred during storage. No clear relationship between the composition of the dispersions, storage conditions and folding/unfolding behaviour was observed. Examination of peak temperatures of PEG 6000 in the solid dispersions stored at 25 °C indicated a slight increase in the peak

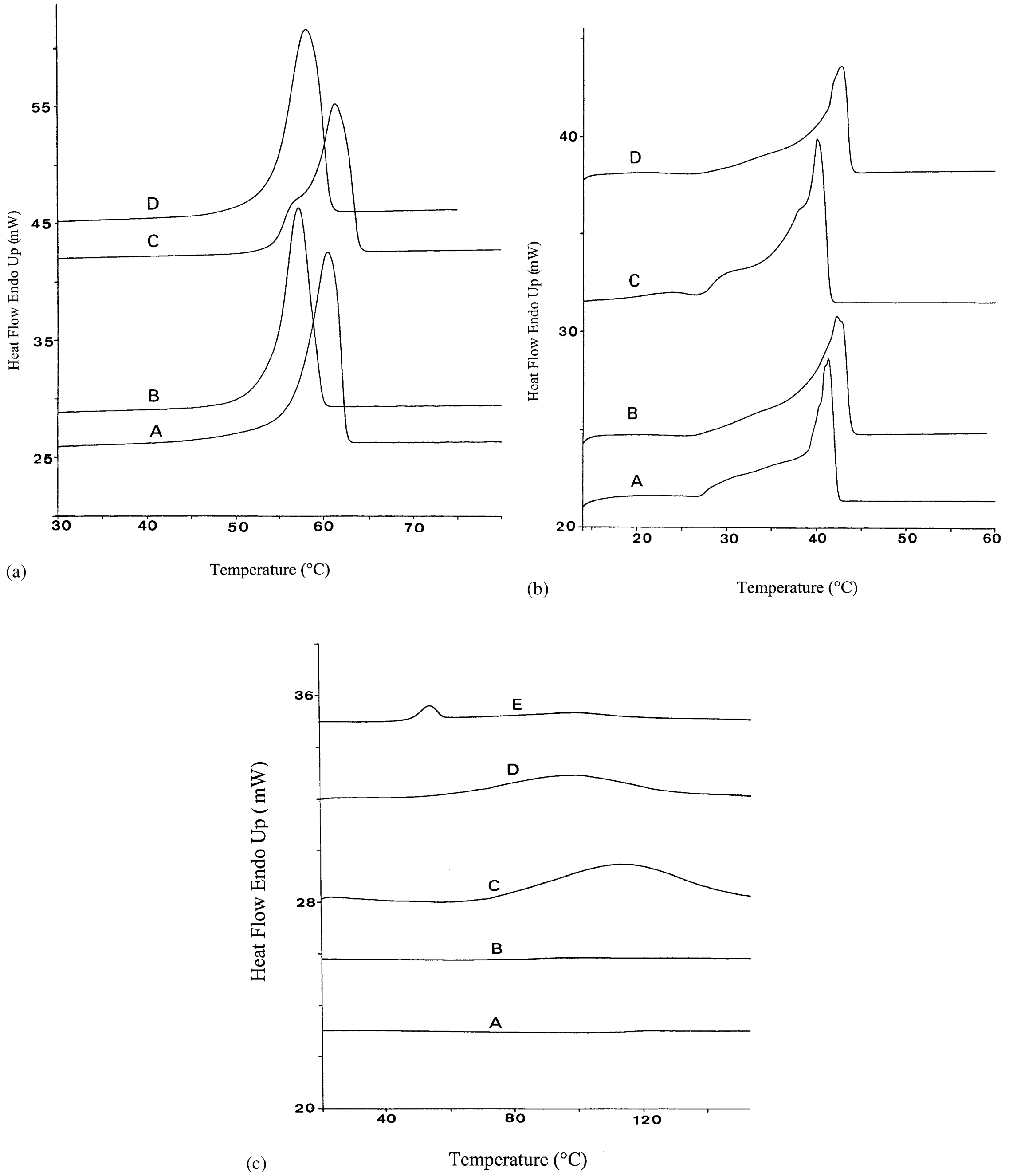


Fig. 2. (a) Representative DSC curves of SDs of UC-781 with PEG 6000 stored at 25 °C: (A) 5% $t = 0$; (B) 20% $t = 0$; (C) 5% $t = 12$; (D) 20% $t = 12$. (b) Representative DSC curves of SDs of UC-781 with Gelucire® 44/14 stored at 25 °C: (A) 5% $t = 0$; (B) 5% $t = 6$; (C) 10% $t = 0$; (D) 10% $t = 6$. (c) Representative DSC curves of SDs of UC-781 with PVP K30 stored at 25 °C: (A) 5% $t = 0$; (B) 10% $t = 0$; (C) 5%, $t = 6$; (D) 10% $t = 6$; (E) 40% $t = 12$. The percentages indicate the concentration of UC-781 in the dispersions by weight, and t represents storage time (months).

temperatures of PEG 6000 as illustrated in Fig. 2(a). On the other hand, there were no marked differences between samples stored at 4–8 °C and those at 25 °C (data not shown). Representative peak temperatures of UC-781 in the solid dispersions of UC-781 with PEG 6000 at 25 °C are shown in Table 1. There was no influence of storage time as well as storage conditions on the peak temperatures of this drug in the solid dispersions. Fig. 3(a) shows representative data for the enthalpy of fusion (ΔH_f) of PEG 6000 in the solid dispersions for some samples stored at 25 °C. The results indicated that storage of solid dispersions of UC-781 with PEG 6000 at 25 °C resulted into a considerable increase in ΔH_f of the carrier even after 2 months, while samples stored at 4–8 °C showed only a small increase in ΔH_f after 2 months (data not shown). Generally, the enthalpy of fusion (ΔH_f) of PEG 6000 in solid dispersions stored at 25 °C after 2, 6, and 12 months was always higher than that of dispersions stored at 4–8 °C. This indicates that at time zero the crystallinity of PEG 6000 was less and gradually increased as a function of time due to the reorganization of the lamellae to a more stable structure, the effect being higher at 25 °C. Similar observations of the enthalpy of fusion of PEG 6000 to increase as a function of time was reported by Dordunoo et al. (1997). On the other hand, the ΔH_f of UC-781 in the solid dispersions with PEG 6000 after storage did not show any marked differences compared to the values obtained at the beginning of the study. The ΔH_f values were more or less the same throughout the study, and there was no clear differences between samples stored at 4–8 °C with those at 25 °C. These observations clearly indicate that the carrier in the solid dispersions is changing as a function of time while the state of the drug is maintained.

Table 1
The effect of storage of SDs of UC-781 with PEG 6000 at 25 °C on the peak temperatures of UC-781 ($t = 0$, 2, 6 and 12 months)

%UC-781	Peak temperature (°C) of UC-781 in the SDs			
	$t = 0$	$t = 2$	$t = 6$	$t = 12$
30	74.7±0.0	74.7±1.1	74.0±0.0	74.4±0.8
40	92.3±0.2	92.1±0.3	91.6±0.4	92.4±0.1
50	106.2±0.3	105.6±0.3	105.3±0.0	106.1±0.4
60	115.4±0.1	115.3±0.1	114.8±0.0	115.9±0.1
70	122.2±1.6	121.9±0.1	121.3±0.0	122.5±0.2
80	126.8±0.1	126.3±0.2	126.0±0.2	126.8±0.1

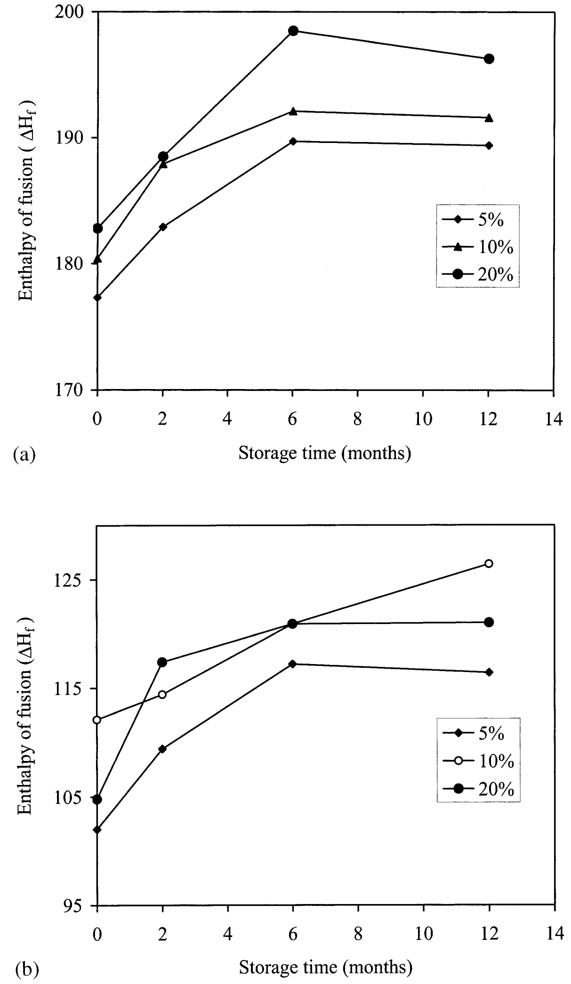


Fig. 3. (a) The effect of storage time on the enthalpy of fusion of PEG 6000 in the SDs of UC-781 with PEG 6000 at 25 °C. (b) The effect of storage time on the enthalpy of fusion of Gelucire® 44/14 in the SDs of UC-781 with Gelucire® 44/14 at 25 °C. The percentages indicate the concentration of UC-781 in the dispersions by weight ($n = 3$).

From the DSC curves of solid dispersions of UC-781 with Gelucire® 44/14 it could be observed that the melting behaviour (peak temperature and enthalpy of fusion) of the carrier significantly changed as a function of storage time (Figs. 2(b) and 3(b)). The peak temperatures and the enthalpy of fusion of Gelucire® 44/14 in the solid dispersions increased as a function of storage time, indicating a reorganization of the structure of the carrier. On the other hand, the storage temperatures had a slight influence on the enthalpy of fusion of Gelucire® 44/14 in the solid dispersions. Opposite to the observation made in Gelucire® 44/14 dispersions, the enthalpy of fusion of pure Gelucire® 44/14 slightly decreased as a function of storage time, while no significant change in its peak melting temperature could be observed. Given the self-emulsifying character of Gelucire® 44/14, uptake of water might be responsible for this decrease in its enthalpy of fusion.

It is known that glyceride based excipients consisting of a mixture of mono-, di-, and triglycerides of natural saturated fatty acids may exhibit ageing effects, whereby physical properties (e.g. melting) change on storage due to the conversion of the triglyceride fraction to a more stable form (Kahela et al., 1987). Gelucire® 44/14 is made up of similar components, therefore it would be expected to have similar properties. Some products formulated with Gelucire® have been found to exhibit ageing effects (Remunan et al., 1992a,b) while other studies have shown no changes in the properties of Gelucire® formulations as a function of time (Dordunoo et al., 1991).

With respect to the DSC curves of SDs of UC-781 with PVP K30, a slight difference between samples stored at different conditions as a function of time was noted. Fig. 2(c) shows representative DSC curves of solid dispersions of UC-781 with PVP K30 stored at 25 °C. A large endotherm due to water evaporation becomes clearly visible in some samples. This endotherm increased as a function of storage time and was more pronounced at lower drug concentrations. The data obtained further demonstrate the absence of endothermic peaks corresponding to the melting of UC-781 in the solid dispersions for up to 12 months. This observation indicated that no recrystallization of UC-781 in the solid dispersions took place during storage, even at higher concentrations of the drug in PVP K30. These findings demonstrate the potential of PVP K30 in suppressing the crystallization of UC-781. The stabilizing effect by PVP K30 observed in this study can be explained by the fact that the glass transition temperature of UC-781 in the solid dispersions was raised significantly compared to that of UC-781 in its pure state. Storage of amorphous drugs at a temperature that is below their glass transition temperature (T_g) is believed to be a contributory factor to their stability (Yoshioka et al., 1995). The molecular mobility of amorphous drugs below the glass transition temperature is negligible or, if present at all, is very low (while above the T_g their molecular mobility is higher). From our previous study, a detailed characterization of molecular dispersions of UC-781 with PVP K30 was performed (Damian et al., 2001a). The carrier was found to form an intermolecular interaction (H-bonding) with UC-781, involving $C=O$ of PVP K30 and NH group of UC-781. The interaction between these two components is thought to play a major role in suppressing the crystallization of the drug during storage. Similar findings of PVP K30 to suppress the crystallization of pharmaceutical compounds were reported by Yoshioka et al. (1995).

3.2. X-ray powder diffraction

It was interesting to observe that the amorphous state of UC-781 in solid dispersions with PVP K30 was maintained throughout the storage period (Fig. 4(a)). The only observation was the slight increase in the intensity of the baseline in the diffraction patterns of PVP K30 in which the baseline at time zero was not as flat as that observed after 12 months. This was the case for samples stored at 4–8 and 25 °C; however, the peaks corresponding to UC-781 could not be detected, which indicates the maintenance of the amorphous state of the drug in solid dispersions. These differences are considered to arise as a result of the changes in the material characteristics of the polymer rather than those of the drug. The data from this section confirm the suitability of PVP K30 in preventing crystallization of UC-781. Similar findings were reported by Thakkar et al.

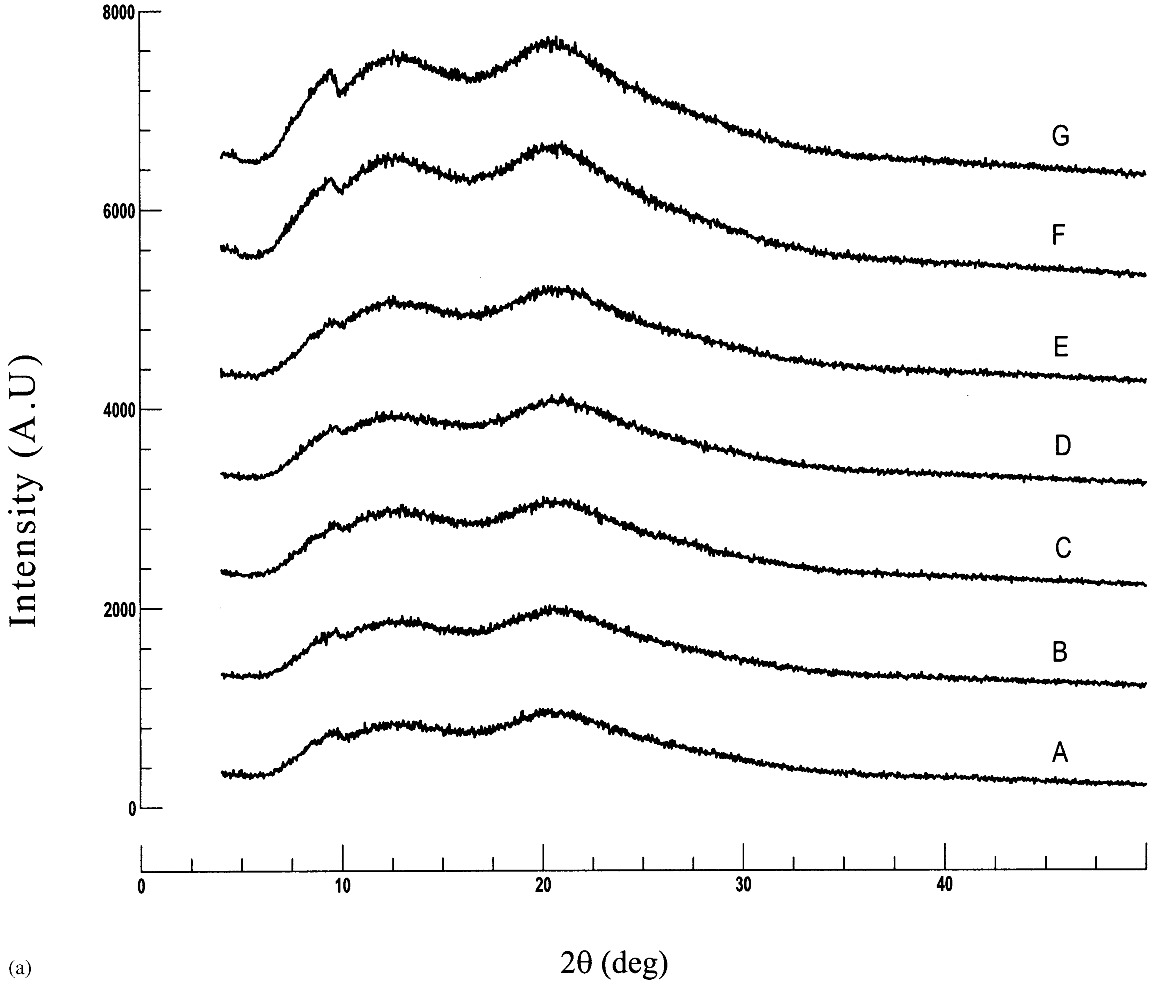
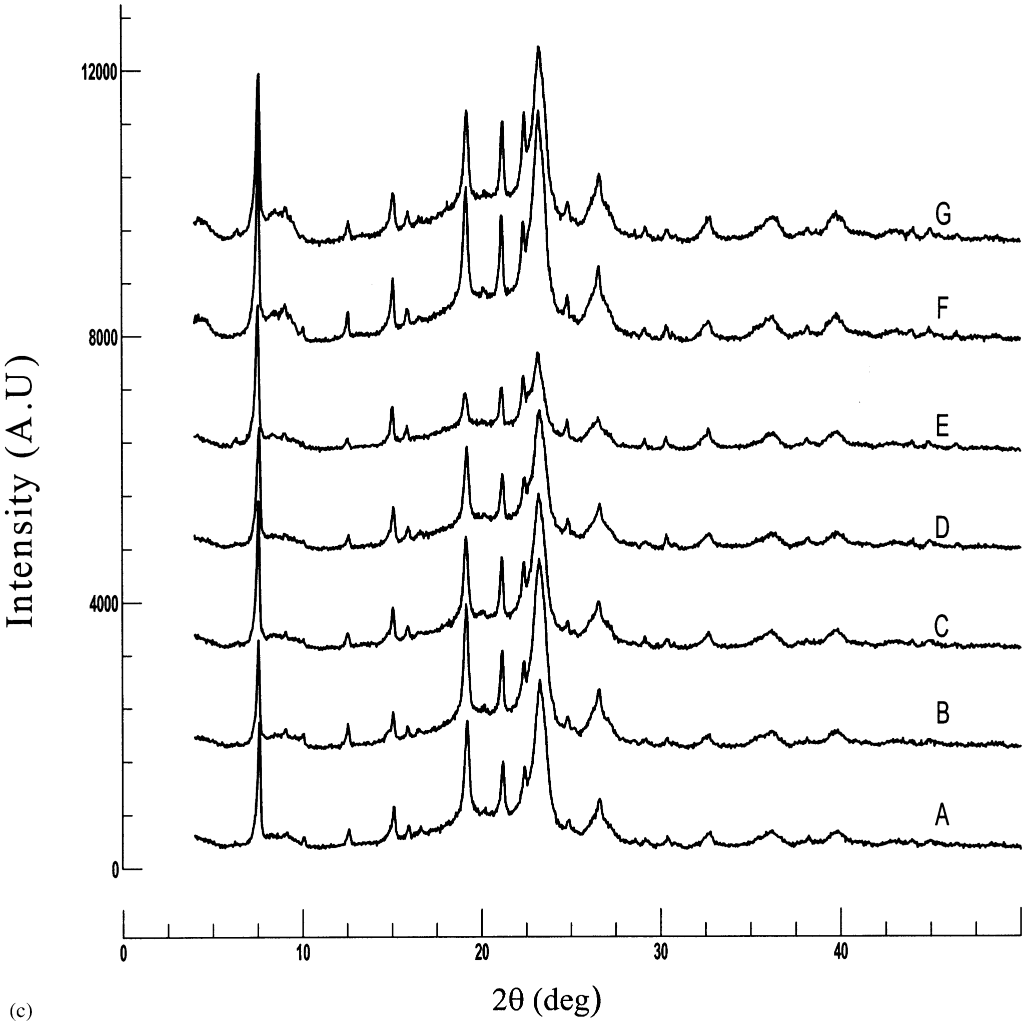


Fig. 4. (a) X-ray powder diffraction patterns of SDs of UC-781 (10% UC-781) with PVP K30 stored at 4–8 and 25 °C: (A) $t = 0$; (B) $t = 2$, 4–8 °C; (C) $t = 2$, 25 °C; (D) $t = 6$, 4–8 °C; (E) $t = 6$, 25 °C; (F) $t = 12$, 4–8 °C; (G) $t = 12$, 25 °C. (b) X-ray powder diffraction patterns of SDs of UC-781 with PEG 6000 (20% UC-781) stored at 4–8 and 25 °C: (A) $t = 0$; (B) $t = 2$, 4–8 °C; (C) $t = 2$, 25 °C; (D) $t = 6$, 4–8 °C; (E) $t = 6$, 25 °C; (F) $t = 12$, 4–8 °C; (G) $t = 12$, 25 °C. (c) X-ray powder diffraction patterns of SDs of UC-781 (10% UC-781) with Gelucire® 44/14 stored at 4–8 and 25 °C: (A) $t = 0$; (B) $t = 2$, 4–8 °C; (C) $t = 2$, 25 °C; (D) $t = 6$, 4–8 °C; (E) $t = 6$, 25 °C; (F) $t = 12$, 4–8 °C; (G) $t = 12$, 25 °C. t represents storage time (months).

(1977) who found that PVP K30 maintained nabilone into its amorphous state for up to 2 years.

Fig. 4(b) shows the typical diffraction patterns of SDs of UC-781 with PEG 6000 (drug concentration 20%) up to 12 months. The spectra were similar and all features of the drug were observed in all samples; the storage time and conditions had no influence on the appearance of the diffraction patterns. However, the differences observed in DSC analysis (the increase in enthalpy of fusion of PEG 6000 in the solid dispersions at 25 °C) could not be detected by X-ray powder diffraction analysis. With respect to Gelucire® 44/14, all features of the drug and the carrier were maintained in the solid dispersions at all conditions. Fig. 4(c) shows a representative X-ray powder diffraction pattern of SDs of UC-781 with Gelucire® 44/14. All peaks from crystalline UC-781 were observed, and were comparable to those



(c)

Fig. 4 (*Continued*)

obtained at time zero at all conditions. The appearance of crystalline peaks of UC-781 at the same positions shows that the crystal parameters of UC-781 in the solid dispersions did not change on storage.

3.3. Dissolution studies

In order to further evaluate the effect of storage conditions on the properties of the solid dispersions under investigation, their dissolution behaviour was studied. A change in physical structure as a result of ageing of solid dispersions will be reflected by the reduction of their dissolution rate as a function of time. Fig. 5(a) shows representative dissolution profiles of solid dispersions of UC-781 with PVP K30 (10% of UC-781) stored at 25 °C for up to 12 months; the data show a significant reduction of the percentage of drug dissolved in the dissolution medium. Similar observations were made for all dispersions of UC-781 with PVP K30 investigated. No clear differences between the samples stored at 4–8 °C with those at 25 °C were observed. Despite the reduction of dissolution rates of these samples, their dissolution profiles were still higher than that of pure drug.

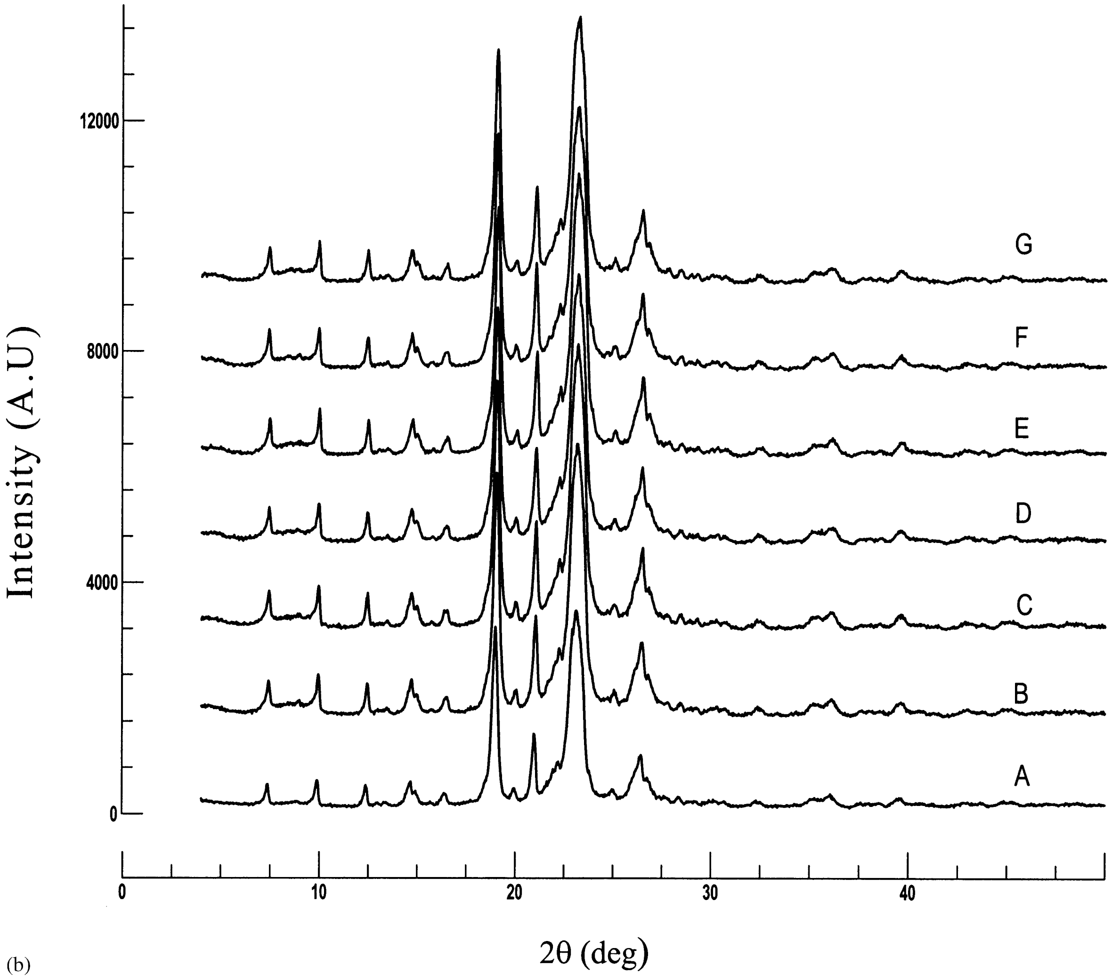


Fig. 4 (*Continued*)

The percentages of UC-781 dissolved from the solid dispersions for all samples after 1 h ranged from 60 to 90%. The reduction in dissolution rate suggests that there is a change in the physical structure of the amorphous UC-781/PVP K30 dispersions, however, these differences were not observed by the data obtained from X-ray powder diffraction. Other researchers (Sugimoto et al., 1980, 1981) reported the reduction in dissolution rates of nifedipine-polyvinylpyrrolidone coprecipitates, the reason being due to the partial crystallization of the amorphous drug in the carrier matrix as the result of the hygroscopic nature of PVP K30. The absence of crystallinity of UC-781 in the solid dispersions with PVP K30 was confirmed by DSC and X-ray powder diffraction. Therefore, changes in the dissolution behaviour cannot be explained in terms of the differences in crystallinity of the drug. In addition, the visual observation from our study showed that the solid dispersions were sticky due to water uptake of the polymer, which is also reflected by the water evaporation endotherm in the DSC curves (Fig. 2(c)). This resulted into the formation of lumps that contributed to slowing down their dissolution properties. Similar observations were made in our laboratory when using PVP K25 to prepare solid dispersions with other compounds.

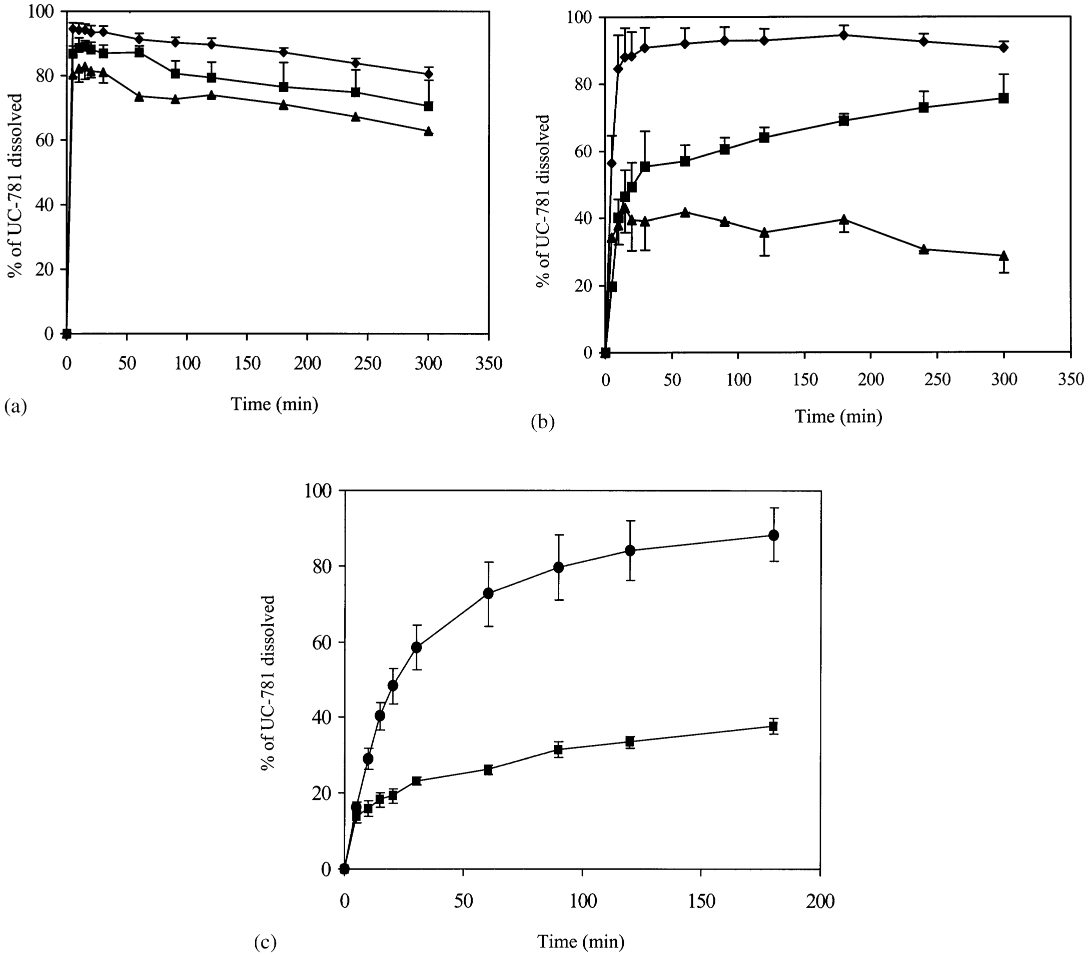


Fig. 5. (a) Dissolution profiles of SDs of UC-781 with PVP K30 (10% w/w) stored at 25 °C for 0, 6 and 12 months: ◆ = 0, ■ = 6 months, and ▲ = 12 months. (b) Dissolution profiles of SDs of UC-781 with Gelucire® 44/14 (5% w/w) stored at 25 °C for 0, 6 and 12 months: ◆ = 0, ■ = 6 months and ▲ = 12 months. (c) Dissolution profiles of SDs of UC-781 with PEG 6000 (20% w/w) stored at 25 °C for 0 and 12 months: ● = 0 and ■ = 12 months.

Comparable behaviour was observed on solid dispersions of UC-781 with Gelucire® 44/14 (Fig. 5(b)) and PEG 6000 (Fig. 5(c)). The solid dispersions again formed lumps that dissolved very slowly compared to the samples analysed at time zero; the remains of the solid dispersions could be visually observed in the dissolution medium after finishing the dissolution experiment. Similar observations of dissolution properties of SDs containing PEG 6000 as a hydrophilic carrier to decrease as a function of storage time were previously reported by Ford and Rubinstein (1979, 1980).

4. Conclusions

The findings of this study have revealed that, the DSC curves of solid dispersions of UC-781 with PVP K30 did not show any melting peaks corresponding to UC-781 after storage. These results confirm the suitability of PVP K30 in preventing the crystallization of UC-781. The stabilization of the amorphous state of UC-781 during storage can be explained to be as a result of elevation of T_g of the drug, and/or the interaction between the drug and the carrier that may then act as a barrier to prevent the free movement of the drug molecules. The DSC data obtained from PEG 6000 and Gelucire® 44/14 showed some variations in their melting peak temperatures and enthalpy of fusion. It was shown that the enthalpy of fusion of PEG 6000 increased after storage; and it was more pronounced for samples stored at 25 °C compared to those at 4–8 °C indicating the reorganization of the crystalline domains of the polymer. An increase in enthalpy of fusion and melting peak temperature of Gelucire® 44/14 in solid dispersions was more pronounced for samples stored at 25 °C. Dissolution of UC-781 from all solid dispersions decreased as a function of storage time. While these observations concurred with the DSC data for all solid dispersions, they were not reflected by X-ray powder diffraction data. This indicates that it is the change of the physical state of the polymers and not that of the drug that is responsible for decreased dissolution properties.

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