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Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30

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Abstract

In order to increase the dissolution of temazepam, solid dispersions were prepared using polyethylene glycol 6000 (PEG 6000) and polyvinylpyrrolidone K30 (PVP K30). Dispersions with PEG 6000 were prepared by fusion-cooling and co-evaporation, while dispersions containing PVP K30 were prepared by co-evaporation. In contrast to the very slow dissolution rate of pure temazepam, the dispersion of the drug in the polymers considerably enhanced the dissolution rate. This can be attributed to improved wettability and dispersibility, as well as particle size reduction and decrease of the crystalline fraction of the drug. The aqueous solubility of temazepam was favoured by the presence of PEG 6000. The negative values of the Gibbs free energy and enthalpy of transfer explained the spontaneous transfer from pure water to the aqueous polymer environment. It was found that temazepam was decomposed in the presence of aqueous solutions of PVP K30 to at least two unidentified degradation products. Drug–polymer interactions in the solid state were investigated using differential scanning calorimetry, X-ray powder diffraction, and fourier-transform infrared spectroscopy. PEG 6000 gave a eutectic system in which liquid polymer could dissolve approximately 10% of temazepam. On the other hand, X-ray powder diffraction patterns and thermal analysis indicated that the drug was in the amorphous state up to a concentration of 40% w/w when dispersed in PVP K30; the infrared spectra indicated solid state interactions between the OH of temazepam and the C=O of PVP K30.

Keywords: Solid dispersion; Differential scanning calorimetry; Dissolution; X-ray powder diffraction; FT–IR; Temazepam

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1. Introduction

Temazepam is a member of the 1,4-benzodiazepine group, and is clinically used in the treatment of anxiety, insomnia, and as an adjuvant for anesthesia (Fraschini and Stankov, 1993). Like other members of the 1,4-benzodiazepine group, it shows poor water solubility and dissolution properties. Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs in general, include micronization (Atkinson et al., 1962), the use of surfactants (Khalafallah et al., 1975), and the formation of solid dispersions (Sekiguchi and Obi, 1961). Chiou and Riegelman (1971) outlined six types of drug–carrier interactions in solid state dispersions: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates in a crystalline carrier, and compound or complex formation. Other factors such as increased wettability, solubilization of the drug by the carrier at the diffusion layer, and the reduction or absence of aggregation and agglomeration may also contribute to increased dissolution.

Among the carriers used in the formation of solid dispersions, polyethylene glycol and polyvinylpyrrolidon are the most commonly used. Both polymers show excellent water solubility and vary significantly in molecular weight, ranging from 200 to in excess of 300 000 for polyethylene glycol and from 10 000 to 700 000 for polyvinylpyrrolidon. The molecular size of both polymers favours the formation of interstitial solid solutions.

The aim of the present study was to evaluate the physicochemical properties of solid dispersions of temazepam in polyethylene glycol 6000 (PEG 6000) and in polyvinylpyrrolidon (PVP K 30). Dispersions with PEG 6000 were prepared by fusion-cooling and co-evaporation, while dispersions with PVP K30 could only be prepared by evaporation. In order to characterize the prepared dispersions, differential scanning calorimetry (DSC), X-ray powder diffraction, Fourier–transform infrared spectroscopy, as well as dissolution and solubility studies were carried out.

2. Materials and methods

2.1. Materials

Temazepam was kindly supplied by Sanico (Turnhout, Belgium). Polyethylene glycol 6000 and polyvinylpyrrolidon K30 (Kollidon K30) were kindly provided by BASF (Ludwigshafen, Germany). All other materials were of analytical or HPLC grade.

2.2. Preparations of solid dispersions and physical mixtures

2.2.1. Physical mixtures

Temazepam and PEG 6000 or PVP K30 were accurately weighed, pulverized and then mixed thoroughly by light trituration during 3 min in a mortar until a homogeneous mixture was obtained. The mixture was passed through a 350 μm sieve. In this way physical mixtures containing from 1 up to 90% w/w of drug in the polymers were prepared.

2.2.2. Solid dispersions prepared by melting of the carrier

Temazepam was added to the melted PEG 6000 at 72°C and the resulting homogeneous preparation was rapidly cooled in a freezing mixture of ice and sodium chloride, and stored in a desiccator for 24 h. Subsequently, the dispersion was ground in a mortar and passed through a 350 μm sieve. The concentration of temazepam (ranging from 1 up to 90% w/w) was determined with HPLC.

2.2.3. Solid dispersions prepared by co-evaporation

Co-evaporated systems containing from 1 up to 90% w/w of temazepam were prepared by dissolving the drug and PEG 6000 or PVP K30 in a minimum amount of purified ethanol. The solvent was then removed rapidly by evaporation under reduced pressure at 40°C. The dispersions were stored in a desiccator for 24 h, ground in a mortar, and passed through a 350 μm sieve. The concentration of temazepam in the dispersions was determined with HPLC.

2.3. Analysis of temazepam

Concentrations of temazepam were determined using an isocratic HPLC method.

The system consisted of a LiChroGraph L-6000 HPLC pump (Merck-Hitachi, Darmstadt, Germany); a Rheodyne Model 7125 Syringe Loading Sample Injector (Rheodyne, Cotati, CA, USA) equipped with a 20 μl loop; a LiChroGraph L-4000 UV detector (Merck-Hitachi, Darmstadt, Germany), set at 254 nm; and a Merck-Hitachi Model D-2500 Chromato-Integrator (Darmstadt, Germany). The 12.5×0.4 cm column was packed with LiChrospher 60 RP-select B (5 μm) (Merck, Darmstadt, Germany). The mobile phase, which consisted of acetonitrile:phosphate buffer (0.05 M; pH 3.0) (46:54; v/v), was filtered through a nylon membrane filter (0.45 μm) and degassed by ultrasonication before use. The flow rate was 1.0 ml/min, and the detection limit was 0.020 ng. The relative standard deviation of the intraday and interday variability was less then 5% ($n = 3$), and 7% ($n = 3$), respectively.

2.4. Dissolution studies

Dissolution studies were performed using USP XXIII apparatus # 2. Samples of pure temazepam, physical mixtures and solid dispersions equivalent to 5 mg of the drug were added to the dissolution medium (1000 ml of demineralized water at a temperature of 37°C), which was stirred with a rotating paddle at 50 rpm. At suitable time intervals, 1 ml samples were withdrawn, filtered (0.22 μm), and analyzed with HPLC. The same volume of fresh medium was replaced and the correction for the cumulative dilution was calculated. Each test was performed in triplicate.

2.5. Solubility measurements

Solubility determination of temazepam in mixtures of water and PEG 6000 or PVP K30 was carried out by adding an excess of drug (50 mg) to 20 ml of demineralized water or to an aqueous solution of the polymers (1; 5; 10; 15% w/v) in sealed glass containers. Three temperatures (24, 34, and 46°C) were tested and each experiment was performed in duplicate. The solutions were rotated in a water bath at a constant temperature for 48 h, after which an aliquot was rapidly filtered through a 0.22 μm membrane. All material used for the filtration was brought to the same temperature as the solutions to prevent precipitation of the drug. Prior to analysis, all samples were diluted with demineralized water. Analysis was performed using HPLC.

2.6. Decomposition kinetics of temazepam in the presence of PVP K30

Degradation of the drug in the presence of PVP K30 solutions was studied by following the disappearance of temazepam as a function of time. The study was conducted at four different temperatures: 4, 25, 40, and 60°C; and at three concentration levels of the polymer: 5, 10, and 15% w/v. Analysis was performed with HPLC and peak purity was checked with photo diode array detection (PDA 990; Waters, Millford, MA).

2.7. Thermal analysis

Differential scanning calorimetry (DSC) measurements were carried out using a Perkin–Elmer DSC-7 differential scanning calorimeter (Perkin–Elmer, Norwalk, CT, USA) equipped with a liquid nitrogen subambient accessory (Perkin–Elmer, Norwalk, CT).

Samples (3–6 mg) were weighed in open aluminum pans and scanned at a speed of 5 or 10°C/min, depending upon the experiment. Pure water and indium were used to calibrate the DSC temperature scale and enthalpic response. Data were treated mathematically using the DSC-7 Analysis program (Perkin–Elmer, Norwalk, CT).

2.8. X-ray diffraction

The physical state of temazepam in the different samples was evaluated with X-ray powder diffraction. Diffraction patterns were obtained on a Philips PW 1050 diffractometer (Bragg–Brentano), with a radius of 173 mm. The Cu Kα radiation (K$\alpha = 1.54184$ Å) was Ni filtered. A

system of diverging, receiving and anti-scattering slits of 1/4°, 0.2 mm, and 1/4° respectively, was used. The pattern was collected with 45 kV of tube voltage and 20 mA of tube current in the angular range $5 < 2\theta < 55°$ in step scan mode (step width 0.04°, counting time 2 s/step).

2.9. Infrared spectroscopy

Fourier–transform infrared (FT–IR) spectra were obtained on a Perkin Elmer 2000 FT–IR system (Perkin–Elmer, Norwalk, CT) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 450–4000 cm^{-1} and the resolution was 1 cm^{-1}.

3. Results and discussion

3.1. Dissolution studies

Fig. 1a and b illustrate the dissolution profiles of pure temazepam, its physical mixtures, and solid dispersions with PEG 6000 and PVP K30, respectively. The time required to dissolve 50% of the drug (T_{50}) was taken as a basis for comparison of the dissolution rate. The results are given in Table 1. It is evident that the rate of dissolution of pure temazepam is very slow, only 50% of the drug is dissolved after 3 h. Dispersion of the drug in the polymers considerably enhanced dissolution. T_{50} values decreased from 3 h for the pure drug to less than 10 min for temazepam–PEG 6000 or temazepam–PVP K30 solid dispersions. The difference in dissolution rate of temazepam–PEG 6000 dispersions prepared either by fusion-cooling or co-evaporation is negligible, as is the difference between dispersions prepared with PEG 6000 and PVP K30. Mechanisms of increased dissolution rate from solid dispersions were reviewed by Ford (1986). A lack of crystallinity, increased wettability, and reduction of drug particle size, were considered to be predominant factors in controlling dissolution.

Table 1
Time required to dissolve 50% of temazepam

Dispersion	% drug	Polymer	T_{50} (min)
FSD	1	PEG	4
FSD	5	PEG	5
FSD	10	PEG	6
SSD	10	PEG	7
SSD	20	PEG	10
MSD	10	PEG	40
SSD	1	PVP	3
SSD	5	PVP	3
SSD	10	PVP	8
MSD	10	PVP	35
Pure temazepam			180

FSD = solid dispersion prepared by fusion-cooling; SSD = solid dispersion prepared by co-evaporation; MSD = physical mixture.

Table 1 shows that increasing the concentration of drug in the dispersions leads to a decrease in dissolution rate. Similar findings were reported with solid dispersions of lorazepam–PEG and ibuprofen–PVP, where a linear relationship was found between the polymer weight fraction and the dissolution rate constant (Najib et al., 1986; Al-Angary et al., 1996). Formation of a polymer outer layer controlling drug release, formation of a continuous drug layer, or release of intact particles from which dissolution occurs over a large area have been proposed to explain similar results (Guyot et al., 1995). These observations stress the importance in finding the optimal drug–carrier ratio in order to achieve the optimal dissolution profile.

Dissolution rate of temazepam from its physical mixtures was significantly higher than for the pure drug. T_{50} values were reached after 40 and 35 min for physical mixtures containing 10%w/w of temazepam in PEG 6000 and PVP K30, respectively. Dry mixing brings the drug in close contact with the hydrophilic polymer and the increased dissolution rate can thus be explained as a result of increased wettability and dispersibility of temazepam. Indeed, during dissolution experiments, it was noticed that physical mixtures immediately sink to the bottom of the dissolution vessel as solid dispersions do, whereas the pure drug floats for a long period on the surface of the dissolution medium.

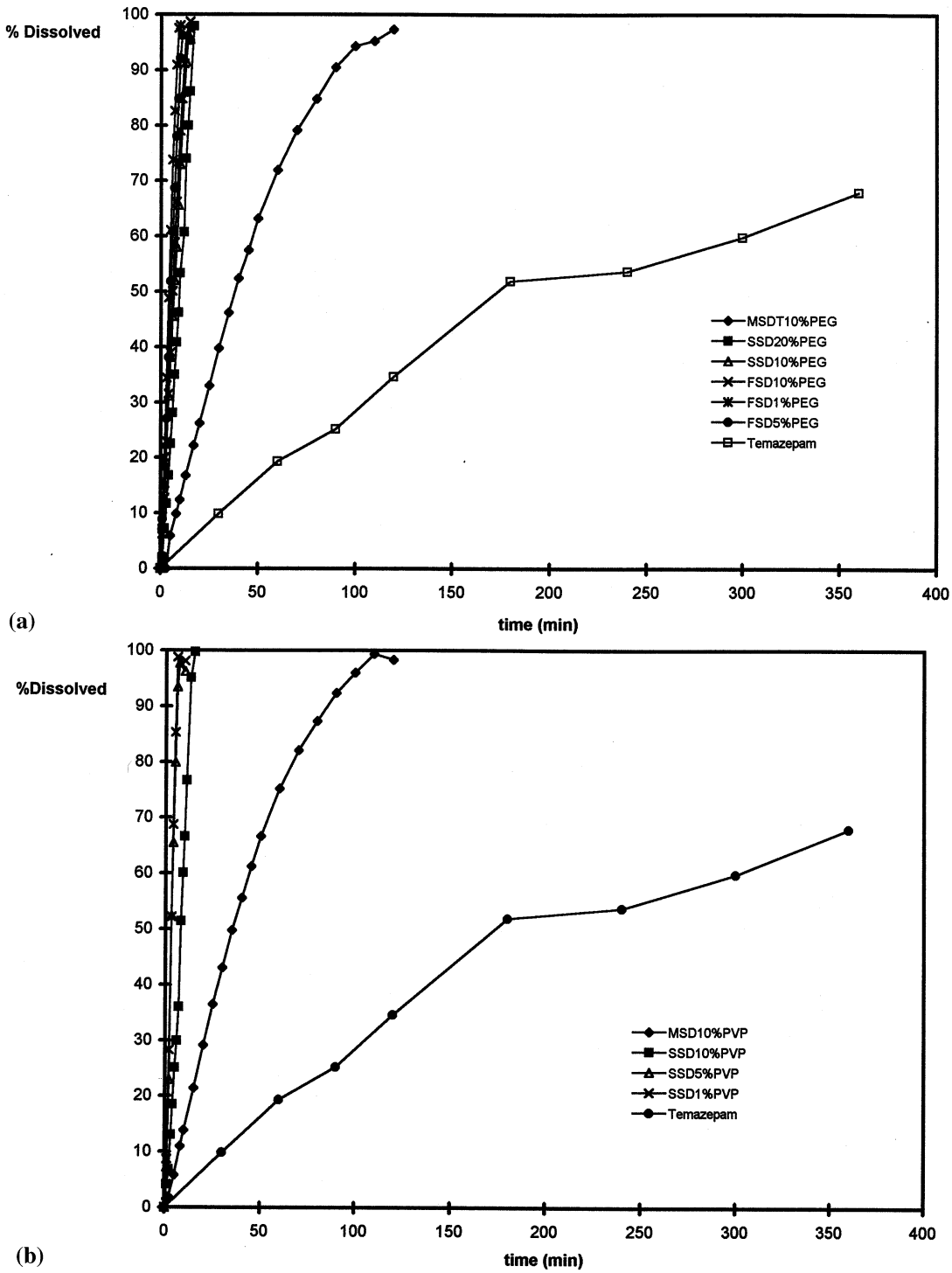

Fig. 1. (a) Dissolution profiles of temazepam, a physical mixture of temazepam/PEG 6000 (MSD) and solid dispersions of temazepam/PEG 6000 (FSD = dispersion prepared by fusion-cooling; SSD = dispersion prepared by co-evaporation. The percentage indicates the amount of temazepam. (b) Dissolution profiles of temazepam, a physical mixture of temazepam/PVP K30 (MSD) and solid dispersions of temazepam/PVP K30 (SSD). The percentage indicates the amount of temazepam.

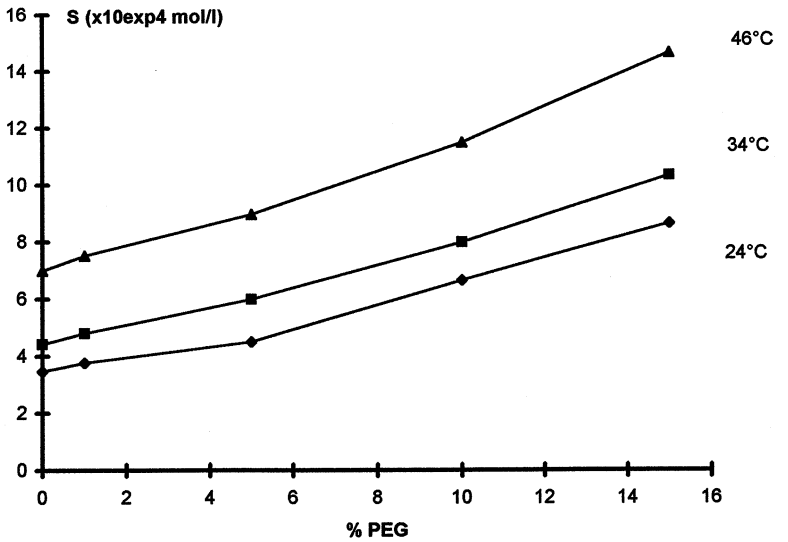

Fig. 2. Solubility (S) diagram of temazepam in water–PEG 6000 mixtures.

3.2. Solubility of temazepam in water–PEG 6000 mixtures

The effect of PEG 6000 on the solubility of temazepam in water is shown in Fig. 2.

To a first approximation, the plots of drug solubility against the polymer concentration at the investigated temperatures indicate a linear relationship in the investigated polymer concentration range. Recently, linearity was observed for the solubility of lorazepam in aqueous solutions of PEG 1500 and PEG 10000; the investigated polymer concentration range was 0–25% (Al-Angary et al., 1996). Solubility of temazepam in pure water at 24°C was $3.46\text{x}10^{-1}$ mM. At the highest polymer concentration (15% w/w), the solubility increased approximately twofold. The same tendency was observed for the other temperatures.

Considering the process of transferring temazepam from pure water to the aqueous solution of PEG 6000, the ratio of the molar solubility of temazepam in aqueous PEG 6000 solution (S_c) towards the molar solubility of the drug in pure water (S_0) can be considered as a partitioning ratio. Therefore, the Gibbs free energy of partitioning or transfer (ΔG_t°) from pure water to the polymer solution can be calculated as follows:

$$\Delta G_t^\circ = -RT \ln \frac{S_c}{S_0}$$

The enthalpy of transfer (ΔH_t°) can be calculated from a modification of the van't Hoff equation:

$$\frac{\mathrm{d} \ln(S_c/S_0)}{\mathrm{d}T} = \frac{\Delta H_t^\circ}{RT^2}$$

Rearanging and solving for ΔH_t° yields

$$\Delta H_t^\circ = -R \frac{\mathrm{d} \ln(S_c/S_0)}{\mathrm{d}(1/T)}$$

Linear regression of $\ln(S_c/S_0)$ versus $1/T$ for PEG 6000 concentrations of 1, 5, 10, and 15% w/v gives a slope equal to $-\Delta H_t^\circ/R$. This treatment assumes that ΔH_t° is reasonably constant over the temperature range studied. In a similar way the heat of solution (ΔH_{sol}°) was calculated.

The thermodynamic parameters given in Table 2 provide further information regarding the increased solubility of temazepam in PEG 6000 solutions. ΔG_t° and ΔH_t° were negative, indicating that the transfer of the drug from pure water to PEG 6000 solutions is spontaneous. Moreover, increasing PEG 6000 concentration leads to a further decrease of ΔH_t° indicating that the process becomes more favourable with higher polymer concentrations.

Table 2
Thermodynamic parameters of the solubility process of temazepam in water–PEG 6000

% PEG 6000	ΔG_t° (J/mol)			ΔH_t° (kJ/mol)	ΔH_{sol}° (kJ/mol)
	24°C	34°C	46°C		
0					25.17
1	−205.4	−205.3	−194.8	−0.354	24.46
5	−803.6	−771.9	−666.8	−2.660	21.99
10	−1614.2	−1508.7	−1324.9	−5.314	19.15
15	−2260.9	−2162.9	−1962.7	−6.200	18.43

Using van't Hoff's law, ΔH_{sol}° was calculated from the solubilities at the different temperatures. The values reported in Table 2 demonstrate that ΔH_{sol}° was always positive but increasing the polymer concentration leads to a decrease in the value of the corresponding ΔH_{sol}° of temazepam. These values only indicate orders of magnitude and must be interpreted as such, because a relative error of 5% on the solubilities brings about a difference of more than 3 kJ/mol in the molar heat of solution. Nevertheless these results indicate that the endothermic effect resulting from the breaking of the self-association bonds is compensated by the exothermic effect resulting from the hydrogen bonds between temazepam and water or the polymer segments. Temazepam possesses one hydrogen donor site, the hydrogen of the OH group, but displays numerous lone pairs of electrons which can in principle act as electron donor. However because of the important electronic delocalization only two of them can be considered as effective: the lone pair of the imine group and one of the lone pairs of the carbonyl group. This means also that the electron donor capacity of the OH group is strongly weakened and that this group will not be significantly inserted in –OH–OH–OH– chains of water or alcohols. However in the liquid phase temazepam is likely to exhibit self-association through hydrogen bonds involving the OH hydrogen donor site of one molecule and one of the two electron donor sites of another molecule. The endothermic heat of solution further explains the increased solubility of the drug with temperature.

3.3. Degradation of temazepam in the presence of PVP K30

When carrying out solubility experiments in the presence of PVP K30, it was observed that temazepam was degraded. Although the apparent solubility of temazepam increased with increasing PVP K30 concentration and temperature, exact solubility could therefore not be calculated. Since it was observed that degradation was more pronounced at higher temperatures and higher polymer concentrations, it was decided to perform a limited study of the decomposition kinetics by following the concentration of the drug at different temperatures and various polymer concentrations.

Fig. 3 shows a representative chromatogram illustrating the decomposition of temazepam in a 10% w/v solution of PVP K 30 at 25°C. Two degradation products can clearly be distinguished. Degradation compound 1 ($R_t = 2.52$ min) is formed rapidly, while the formation of degradation compound 2 ($R_t = 4.32$ min) is more slowly. Photo diode array detection indicated peak purity of both degradants. The characteristic absorption shoulder present at 230 nm in the uv spectrum of temazepam is missing in the spectrum of both degradation products, but the decrease in uv absorbance was more pronounced for degradation compound 2. Preliminary mass spectral data suggest that degradation compound 1 could be the result of a hydrolysis occuring at the imine nitrogen.

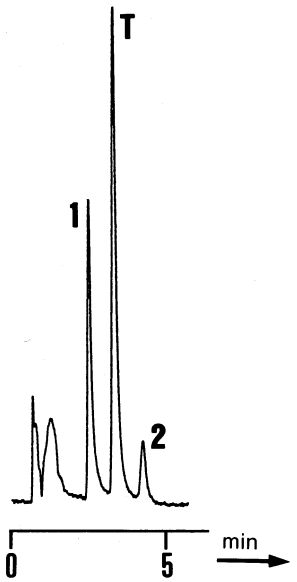

Fig. 3. Chromatogram of temazepam dissolved in 10% w/v PVP K30 at 25°C after 10 days. T = temazepam; D1 = degradant 1; D2 = degradant 2.

The degradation could be described using first order kinetics. The observed first order rate constant (k_{obs}) was calculated from the slope of the least square linear regression line of a plot of ln (C_t/C_0) versus time; C_0 represents the initial concentration of drug and C_t is the concentration at time t.

The observed rate constant was 60 times higher at 60°C compared to 4°C for solutions containing 10% w/v of polymer (Table 3). Increasing the polymer concentration from 5 to 10% leads to a higher degradation rate, but a further increase to 15% does not lead to a significantly higher degradation. This indicates that degradation increases with PVP K30 concentration, and levels off at a certain polymer concentration. From the Arrhenius equation, the activation energy (E_a) was calculated to be 14.02 kJ/mol.

Table 3
Kinetic parameters of the degradation of temazepam in the presence of PVP K30 solutions

% PVP K30	T (°C)	k_{obs} (h^{-1})	$t_{1/2}$ (h)	E_a
10	4	7.07×10^{-4}	980.2	
10	25	2.82×10^{-3}	245.7	
10	40	8.65×10^{-3}	80.1	
10	60	4.20×10^{-2}	16.5	
5	60	2.81×10^{-2}	24.7	
15	60	4.38×10^{-2}	15.7	
				14.02 kJ/mol

3.4. Thermal analysis

The DSC curve of pure temazepam exhibited a single endothermic response corresponding to the melting of the drug. Onset of melting was observed at 159.4 ($\pm$ 0.3)°C, the corresponding heat of fusion (ΔH_f) was 90.9 ($\pm$ 3.2) J/g. When samples of the drug were melted, rapidly cooled to $-$ 5°C at a rate of 100°C/min, and subsequently rescanned at 3°C/min, the melting endotherm disappeared, instead a glas transition was recorded at 66.1 ($\pm$ 1.6)°C. In a recent publication by Dordunoo et al. (1997), the glass transition temperature of temazepam was reported to be 70°C. The difference can probably be explained by the different scanning rate applied, which was 10°C/min.

In all the experiments only a single endotherm exhibiting a shoulder on the leading edge was observed in the DSC curve of pure PEG 6000. According to Craig and Newton (1991), the shoulder may indicate the presence of more than one crystal form within the sample due to grinding effects. Melting of untreated PEG 6000 occurred at 61.9($\pm$ 0.2)°C, ΔH_f was calculated to be 188.6($\pm$ 4.1) J/g. Heating the polymer to 72°C, followed by ice cooling, reduced the melting point with 1.3($\pm$ 0.2)°C. It was suggested that the endotherm of the untreated PEG 6000 corresponds with the extended chain crystal, while the peak of the treated sample corresponds to the once folded chain (Craig and Newton, 1991). Depending upon the molecular weight (M_n), PEG can exhibit several transitions which are attributed to the melting of different crystal structures of the polymer: extended chains (M_n 4000), extended and folded chains ($M_n \simeq 6000$), and folded chains ($M_n \geq 6000$) (Ford and Timmins, 1989). PEG with $M_n = 6000$ showed one transition when crystallized at above 55°C, but two transitions when

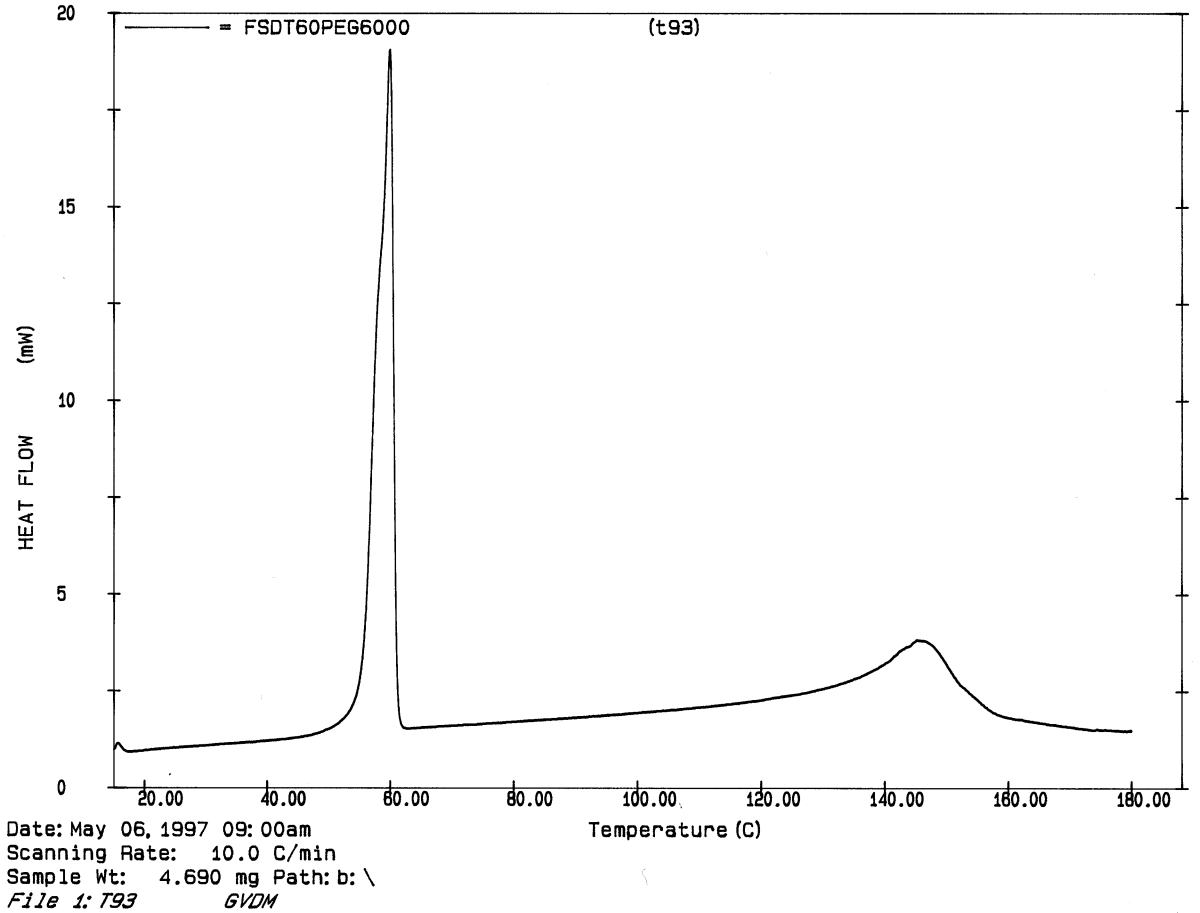

Fig. 4. DSC thermogram of a solid dispersion of temazepam/PEG 6000 (60:40; w/w) prepared by fusion-cooling.

crystallized at below 55°C. The lower transition corresponds to the melting of the once folded chain crystals, whereas the higher transition corresponds to the melting of the extended chain crystals.

During scanning of PVP K30, a broad endotherm ranging from 80 to 120°C was observed, due to the presence of water. Repeated scanning led to the disappearance of the endotherm.

Binary mixtures of temazepam and PEG 6000, whether prepared by physical mixing, fusion-cooling, or co-evaporation always exhibited the same two endothermic transitions corresponding to the melting of the polymer (lower temperature transition) and of the drug (higher temperature transition) (Fig. 4). These similarities suggest the absence of chemical interactions between both species.

Since difficulties were encountered to detect the onset of endothermic transitions in binary mixtures with a low drug content, peak melting points were used to construct the binary phase diagram (Fig. 5).

All mixtures showed a constant melting at approximately 60.5($\pm$0.3)°C, corresponding to the melting of the polymer. These data were used to construct the solidus line. The presence of temazepam in the dispersions hardly affected the melting point of PEG 6000. On the other hand, a small amount of PEG 6000 caused depression of the melting point of the drug. The rising liquidus curve of the phase diagram corresponds to the solubility of temazepam in the liquid polymer. Hot-stage microscopy confirmed that increasing

amounts of drug could be dissolved with increasing temperature, indicating complete miscibility in the liquid state. From the phase diagram it is apparent that approximately 10% of temazepam can be dissolved in the polymer at its melting point, independent of the preparation mode. Similar findings were reported by Kaur et al. (1980). They suggested that phase diagrams of this type have to be considered as a eutectic in which the liquidus (melting point curve of the drug) and the solidus (melting point curve of the polymer) have become superimposed.

DSC thermograms of binary physical mixtures of temazepam and PVP K30 always showed the melting peak of the drug at 160°C and the broad endotherm due to the presence of water ranging from 60 to 120°C. Even at concentrations of 1% w/w, the drug was detectable. Solid dispersions of temazepam and PVP K30 showed the broad endotherm due to the presence of water, but the melting of the drug was no longer observed up to a concentration of 40% w/w of the drug in the polymer (Fig. 6). Solid dispersions containing 50% w/w or more of temazepam exhibited both endotherms. This indicates that temazepam is no longer present as a crystalline material when its concentration does not exceed 40% w/w, but is converted into the amorphous state. As a consequence of the evaporation of the solvent during the preparation of the solid dispersions, viscosity increases very rapidly leading to a decrease in drug mobility. When the solvent is evaporated completely, drug molecules are frozen in the polymer matrix. A crystal latice is not formed, but the drug molecules are randomly 'ordered' comparable to the liquid state and exhibit short range order over only a few molecular dimensions.

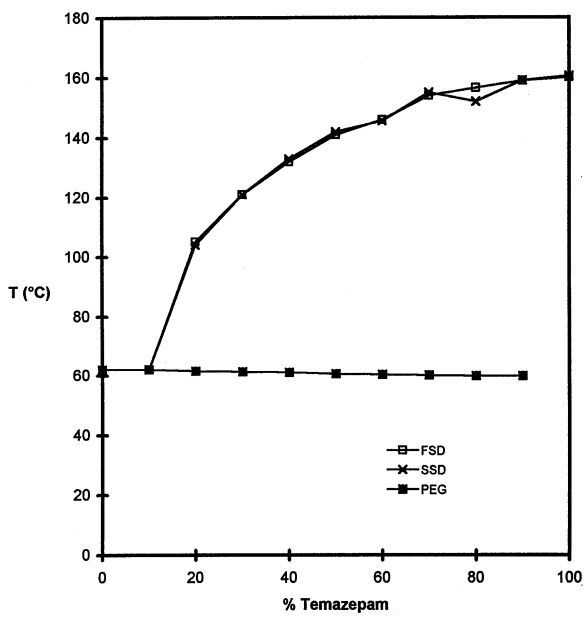

Fig. 5. Phase diagram of binary solid dispersions temazepam/PEG 6000. FSD = dispersion prepared by fusion-cooling; SSD = dispersion prepared by co-evaporation.

3.5. X-ray powder diffraction

The presence of numerous distinct peaks in the X-ray diffraction spectrum indicate that temazepam is present as a crystalline material with characteristic diffraction peaks appearing at a diffraction angle of 2θ at 8.88, 10.34, 11.77, 13.99, 18.95, 20.60, 23.51, and 28.70. PEG 6000 also exhibited a distinct pattern with diffraction peaks at 2θ at 15.00, 18.95, and 23.10, but the spectrum of PVP K30 was characterized by the complete absence of any diffraction peak.

Physical mixtures and solid dispersions of temazepam and PEG 6000 either prepared by fusion-cooling or co-evaporation showed the same diffraction pattern. Up to a content of 10% w/w, none of the diffraction peaks of the drug could be detected. Increasing the drug concentration from 10 up to 80% w/w, the diffraction pattern of temazepam became more distinct. Although the drug was completely dissolved in the melted carrier up to a concentration of 10% w/w and quench-cooled, it could not be concluded from these observations that the drug was amorphous below a concentration of 10% w/w, and the similarity in the diffraction peaks of temazepam in both the physical mixtures and the solid dispersions indicate a negligible solubility of the drug in the solid state. Moreover, no other peaks than those which could be assigned to pure temazepam and PEG 6000 were detected in the fusion-cooled and co-evaporated dispersions indicating no chemical interactions in the solid state between the two entities.

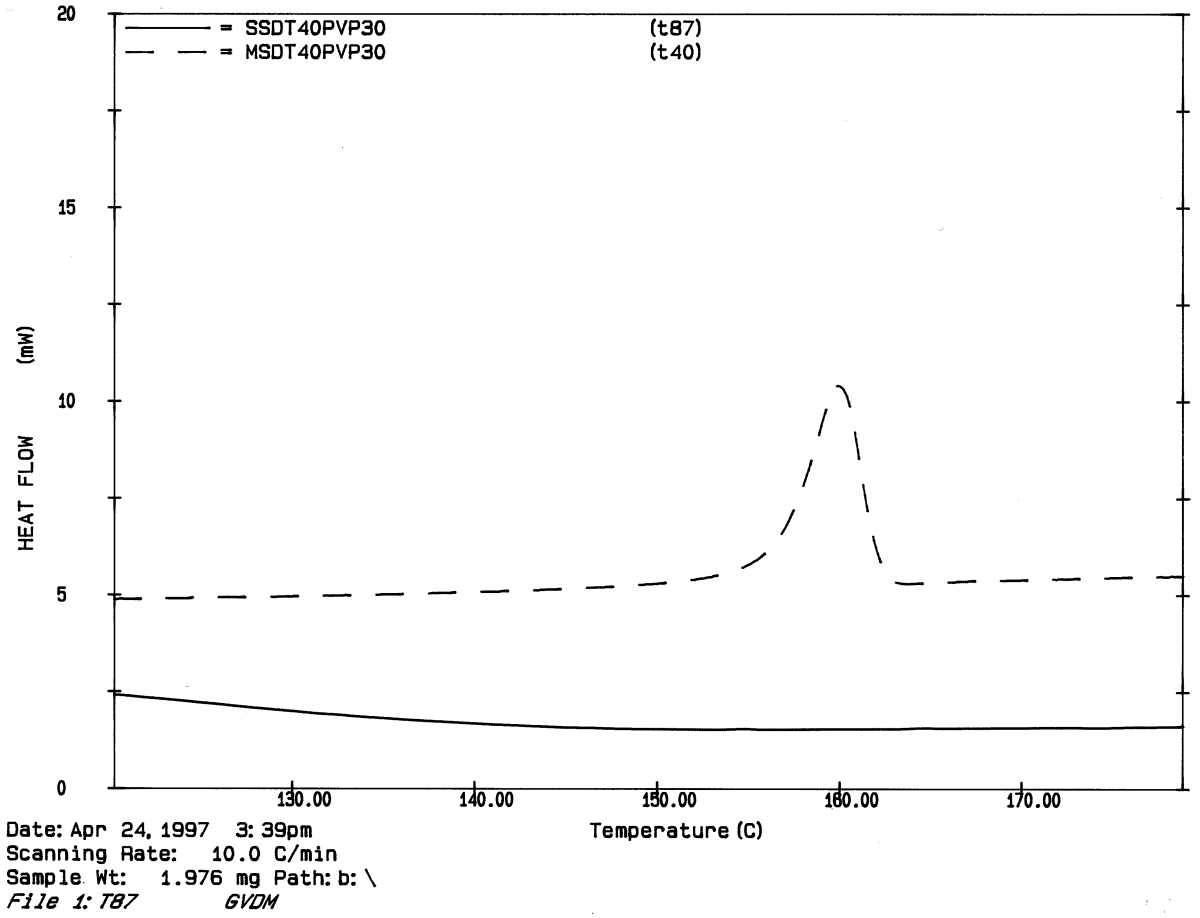

Fig. 6. DSC thermograms of a solid dispersion temazepam/PVP K30 (40:60; w/w) (SSDT40PVP30) and a physical mixture with the same composition (MSDT40PVP30).

Several diffraction peaks attributable to temazepam could be detected in physical mixtures with PVP K30 when the concentration of the drug exceeded 10% w/w. However, in the co-evaporate, up to a concentration of 40% w/w, diffraction peaks of the drug could not be distinguished from the noise indicating that temazepam was in the amorphous state (Fig. 7). These findings concur with the data of the thermal analysis, where up to 40% w/w of temazepam, no endotherm due to melting could be detected. From 50% w/w on, the characteristic peaks of the drug reappeared and increased with increasing drug concentration in the dispersions.

3.6. Fourier–transform infrared spectroscopy

In order to further characterize possible interactions between the drug and the polymeric carrier in the solid state, infrared spectra were recorded. The spectrum of temazepam showed three characteristic bands of the OH group which were found at 3451 cm^{-1} (free OH), 3400 cm^{-1} (OH involved in intramolecular hydrogen bonding with C=O), and 3202 cm^{-1} (OH involved in intermolecular association). The carbonyl stretching mode appears as a very strong Fermi doublet at 1689 cm^{-1} and 1670 cm^{-1}. Other characteristic bands were found at 1605 cm^{-1} (imine) and 1114

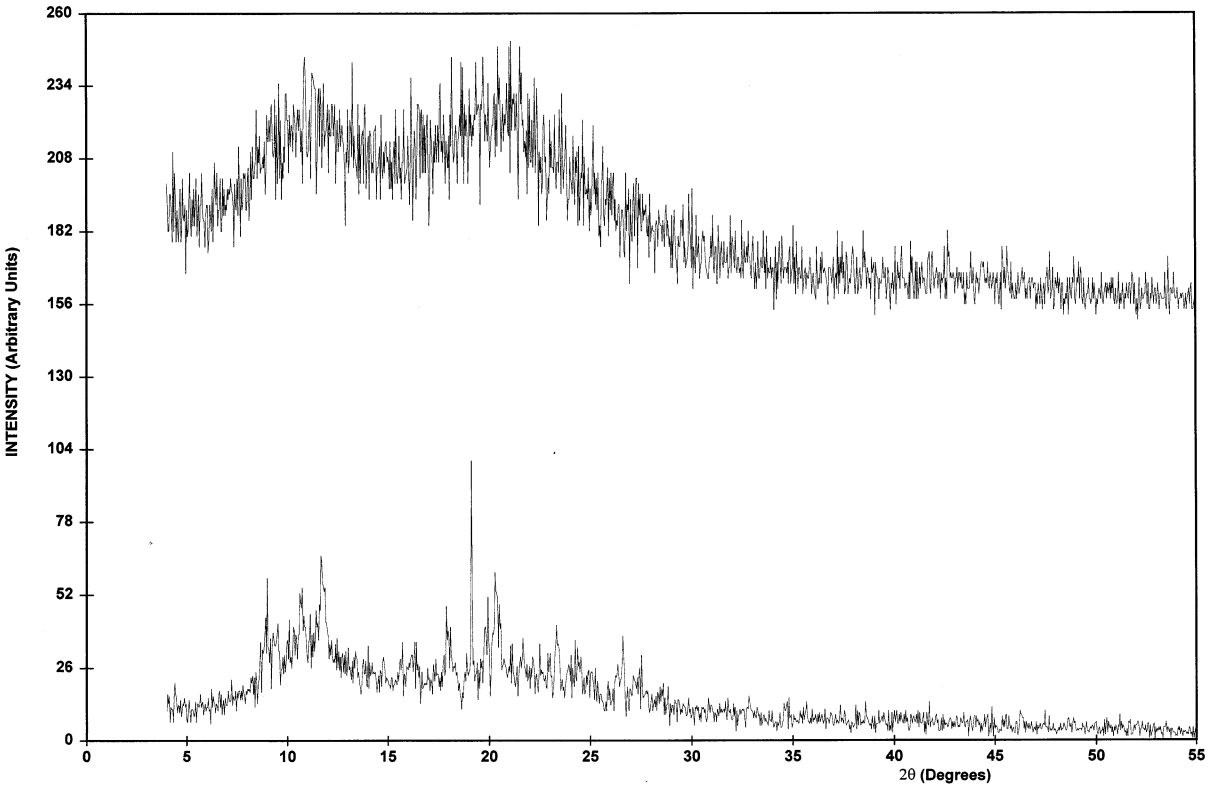

Fig. 7. X-ray powder diffraction spectra of a solid dispersion temazepam/PVP K30 (40:60; w/w) (upper spectrum), and a physical mixture with the same composition (lower spectrum).

cm^{-1} (C–OH stretch). The spectrum of PVP K30 showed, amongs others, important bands at 2953 cm^{-1} (C–H stretch) and 1652 cm^{-1} (C=O). A very broad band was also visible at 3446 cm^{-1} which was attributed to the presence of water confirming the broad endotherm detected in the DSC experiments. Important vibrations detected in the spectrum of PEG 6000 are the C–H stretching at 2890 cm^{-1} and the C–O (ether) stretching at 1110 cm^{-1}.

Comparing the spectra of solid dispersions of temazepam and PEG 6000 prepared by fusion-cooling or co-evaporation and physical mixtures, no difference was shown in the position of the absorption bands. The spectra can be simply regarded as the superposition of those of temazepam and PEG 6000. Although it could be expected to have hydrogen bonding between the hydrogen atom of the OH of the drug and one of the lone pairs of the oxygen atom in PEG 6000, this could not be demonstrated.

When interaction is expected between temazepam and PVP K30 in the solid state, it should reasonably involve the alcohol function of temazepam and the carbonyl group of the polymer in hydrogen bonding. As can be seen in Fig. 8 which shows the spectra of a 10% w/w solid dispersion in comparison with a physical mixture, this is the case. Indeed, the absorption bands which can be assigned to the free OH and the OH involved in intramolecular hydrogen bonding disappeared, and the band due to intermolecular association increased in intensity. The peaks which were assigned to the amide at 1689 and 1670 cm^{-1}, also disappeared, instead a large band was detected. The reason for this observation can be interpreted as a consequence of hydrogen bonding between OH of temazepam and C=O of

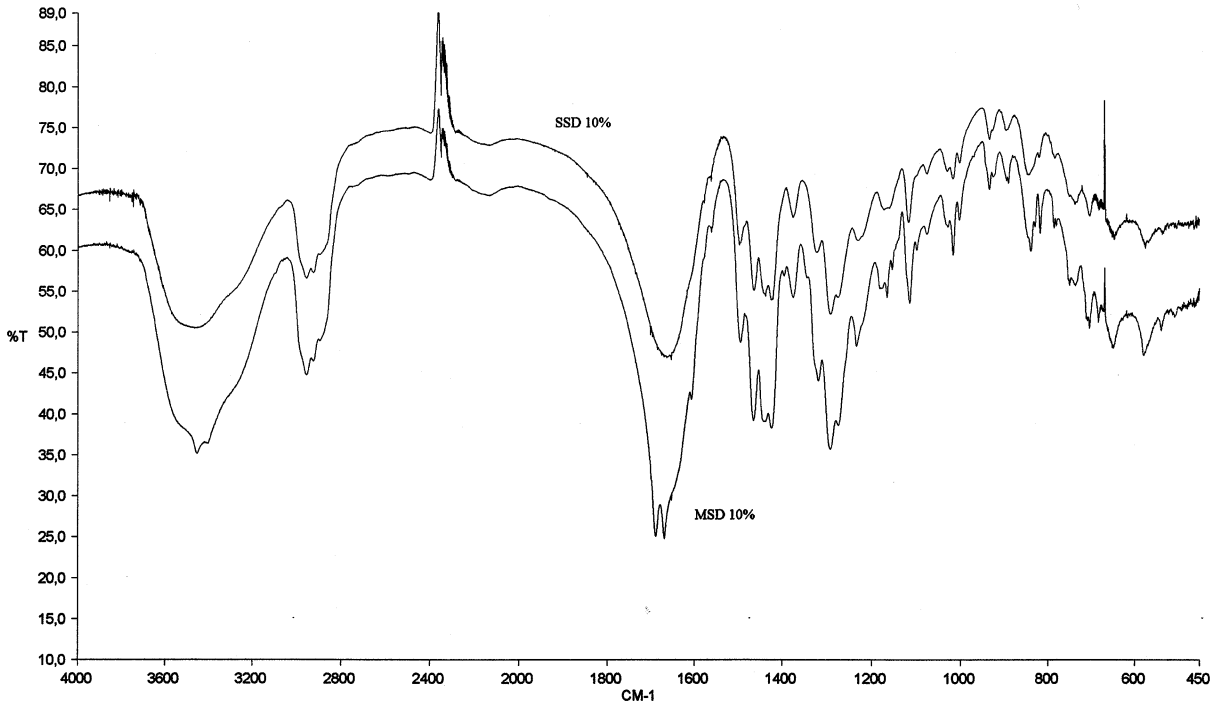

Fig. 8. FT–IR spectra of a solid dispersion temazepam/PVP K30 (10:90; w/w) (SSD10%) and a physical mixture with the same composition (MSD10%).

PVP K30, since hydrogen bonding is thought to influence the bonding strength between the carbon and the oxygen atom of the carbonyl function of temazepam, moving the electron density towards the oxygen atom. This will result in a decrease of ν. Further evidence for the involvement of the carbonyl function of the drug in interaction is given by the disappearance of the band assigned to the out of plane deformation (γCO at 648 cm^{-1}). Other bands which decreased in intensity, or even disappeared from the spectrum of the solid dispersion are: C=N stretch (1605 cm^{-1}), in plane deformation of CH_3 (symmetrical:1344 cm^{-1}; asymmetrical: 1395 cm^{-1}), N–CH_3 stretch (1317 cm^{-1}), C–C–N stretch (1164 cm^{-1}), C–OH stretch (1114 cm^{-1}), CH_3 rocking (1153 cm^{-1}), N–C–C stretch (837 cm^{-1}), C–N–C stretch (817 cm^{-1}).

4. Conclusion

In this paper we showed the increased dissolution rate of temazepam when dispersed in PEG 6000 and PVP K30. Solid dispersions demonstrated a higher dissolution rate than physical mixtures. X-ray powder diffraction and thermal analysis indicated that the drug was amorphous up to a concentration of 40%w/w when dispersed in PVP K30. In this system, drug–polymer interaction through intermolecular hydrogen bonding was demonstrated using FT–IR. The increased dissolution rate in systems containing PEG 6000 was probably the result of increased wettability and dispersibility of temazepam, since no interactions in the solid state could be demonstrated. Solubility studies showed a solubilizing effect of PEG 6000 on temazepam. The negative values of

the Gibbs free energy and enthalpy of transfer from water to an aqueous solution of PEG 6000 indicated the spontaneity of the transfer. Increased solubility was also observed in aqueous solutions of PVP K30, but at the same time, degradation of the drug occurred.

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