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Mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions

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Abstract

Solid dispersion literature, describing the mechanism of dissolution of drug–polyethylene glycol dispersions, still shows some gaps; (A) only few studies include experiments evaluating solid solution formation and the particle size of the drug in the dispersion particles, two factors that can have a profound effect on the dissolution. (B) Solid dispersion preparation involves a recrystallisation process (which is known to be highly sensitive to the recrystallisation conditions) of polyethylene glycol and possibly also of the drug. Therefore, it is of extreme importance that all experiments are performed on dispersion aliquots, which can be believed to be physico-chemical identical. This is not always the case. (C) Polyethylene glycol 6000 (PEG6000) crystallises forming lamellae with chains either fully extended or folded once or twice depending on the crystallisation conditions. Recently, a high resolution differential scanning calorimetry (DSC)-method, capable of evaluating qualitatively and quantitatively the polymorphic behaviour of PEG6000, has been reported. Unraveling the relationship between the polymorphic behavior of PEG6000 in a solid dispersion and the dissolution characteristics of that dispersion, is a real gain to our knowledge of solid dispersions, since this has never been thoroughly investigated. The aim of the present study was to fill up the three above mentioned gaps in solid dispersion literature. Therefore, physical mixtures and solid dispersions were prepared and in order to unravel the relationship between their physico-chemical properties and dissolution characteristics, pure drugs (diazepam, temazepam), polymer (PEG6000), solid dispersions and physical mixtures were characterised by DSC, X-ray powder diffraction (Guinier and Bragg-Brentano method), FT-IR spectroscopy, dissolution and solubility experiments and the particle size of the drug in the dispersion particles was estimated using a newly developed method. Addition of PEG6000 improves the dissolution rate of both drugs. Mechanisms involved are solubilisation and improved wetting of the drug in the polyethylene glycol rich micro-environment formed at the surface of drug crystals after dissolution of the polymer. Formulation of solid dispersions did not further improve the dissolution rate compared with physical mixtures. X-ray spectra show that both drugs are in a highly crystalline state in the solid dispersions, while no significant changes in the lattice spacings of PEG6000 indicate the absence of solid solution formation. IR spectra show the absence of a hydrogen bonding interaction between the benzodiazepines and PEG6000. Furthermore, it was concluded that the reduction of the mean drug particle size by preparing solid dispersions with

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PEG6000 is limited and that the influence of the polymorphic behavior of PEG6000 (as observed by DSC) on the dissolution was negligible.

Keywords: Solid dispersion; PEG6000; Benzodiazepines; Dissolution; Differential scanning calorimetry; X-ray powder diffraction; FT-IR spectroscopy; Solubility; GPC; Particle size determination

1. Introduction

Many potential drug candidates are characterised by a low oral bioavailability. Often, poor drug dissolution/solubility rather than limited permeation through the epithelia of the gastrointestinal tract are responsible for low oral bioavailability. Among the techniques to increase aqueous solubility/dissolution rate, the formulation of solid dispersions is one of the most popular ones (Chiou and Riegelman, 1971; Ford, 1986), although few marketed products rely on this concept. Low molecular weight polyoxyethylene ($Mw < 20\,000$, commonly referred to as polyethylene glycol) has frequently been used as carrier in solid dispersion formulations (Doshi et al., 1997; Trapani et al., 1999; Damian et al., 2000; Franco et al., 2001; Zerrouk et al., 2001a; Abdul-Fattah and Bhargava, 2002). Numerous attempts to understand the physico-chemical principle behind the improvement of the dissolution of drugs by solid dispersion formulation with polyethylene glycols have been reported (Corrigan and Timoney, 1976; Ford and Rubinstein, 1978; Sjökvist and Nyström, 1988; Dordunoo et al., 1991; Craig and Newton, 1992; Sjökvist Saers and Craig, 1992). Mechanisms suggested to be responsible for the improved aqueous solubility/dissolution properties of solid dispersions include reduction of the particle size of the incorporated drug, (partial) transformation of the crystalline drug to the amorphous state, formation of solid solutions, formation of complexes, reduction of aggregation and agglomeration, improved wetting of the drug and solubilisation of the drug by the carrier at the diffusion layer (Corrigan, 1985; Ford, 1986; Craig, 1990). It is highly acceptable, that often more than one of these phenomena determine the rate and extent of dissolution. Therefore, Bragg-Brentano powder diffractometry, differential scanning calorimetry (DSC), infrared spectroscopy, solubility and dissolution experiments are routinely used to study the relationship between dissolution and the physico-chemical state of solid dispersions. Transformation of crystalline drug or semicrystalline polyethylene glycol to the amorphous state and formation of polymorphic drug forms can be detected by Bragg-Brentano powder diffractometry. Differential scanning calorimetry offers the possibility to evaluate the crystallinity of both drug and polymer phases and to characterise polymorphic and amorphous phases. Infrared spectroscopy reveals crystallographic changes of drug and polymer and interactions between drug and polymer molecules, such as hydrogen bonds which are indicative of complex formation. Equilibrium solubilities of the drug in aqueous polymer solutions of different polymer concentrations reveal the solubilisation capacity of the polymer for the drug. Several decades of research on polyethylene glycol–drug solid dispersion systems resulted in a vast amount of valuable information. The physico-chemical phenomena which could be responsible for the improved dissolution of solid dispersions containing PEG6000 are well known and studied. However, the literature still shows some important gaps; (A) only few reports include X-ray diffraction experiments studying solid solution formation (by evaluating the polyethylene glycol lattice spacings) (Sjökvist et al., 1989; Sjokvist et al., 1991; Alden et al., 1994; Damian et al., 2000; Zerrouk et al., 2001b) and only few reports include experiments trying to measure or estimate the particle size and distribution of the drug in the drug–polyethylene glycol dispersion particles (Sjökvist and Nyström, 1988; Sjökvist et al., 1989; Sheu et al., 1994; Dordunoo et al., 1997), although drug particle size reduction is probably an important factor influencing dissolution. Furthermore, to the best of our knowledge, no

polyethylene glycol 6000-drug dispersion has been subject of a study, using all the above mentioned techniques to thoroughly characterise the interplay between dissolution and the different dissolution influencing phenomena possible. (B) Solid dispersion preparation involves recrystallisation of PEG6000, irrespective of the preparation method (solvent or fusion method) used, and the drug can also recrystallise. It is generally accepted, that the crystallisation conditions (in the specific situation of dispersions for example; drug–polyethylene glycol ratio, fusion temperature, time at fusion temperature, batch size, cooling conditions, type and amount of solvent used, storage conditions and time,...) have an important impact on the physical state of the resulting dispersions and hence probably also on the dissolution characteristics of these dispersions. Therefore, it is extremely important that all experiments are performed on dispersion aliquots, which can be believed to be physico-chemical identical. This is not always the case and this makes concluding which phenomenon (or phenomena) is (or are) really responsible for the observed improved dissolution of that particulate dispersion really difficult, since it is possible that the experiments were performed on physico-chemical significant different solid dispersion samples. (C) PEG6000 crystallises forming lamellae with chains either fully extended (0) or folded once (1) or twice (2) depending on the crystallisation conditions (Buckley and Kovacs, 1975, 1976). Recently, a high resolution DSC-method, capable of evaluating qualitatively and quantitatively the polymorphic behaviour of PEG6000, has been reported (Verheyen et al., 2001). Unraveling the relationship between the polymorphic behavior of PEG6000 in a solid dispersion and the dissolution characteristics of that dispersion, is a real gain to our knowledge of solid dispersions, since this has never been thoroughly investigated.

The aim of the present study was to fill up the three gaps in solid dispersion literature mentioned above. Therefore, temazepam and diazepam, members of the 1,4-benzodiazepine group, showing poor aqueous solubility and dissolution, were selected as model drugs. Physical mixtures and solid dispersions prepared by the solvent evaporation method and the fusion method were characterised by solubility and dissolution studies, X-ray powder diffractometry (Bragg-Brentano and Guinier method), Fourier-transform infrared spectroscopy, differential scanning calorimetry and the drug particle size was estimated by a newly developed method in order to unravel the relationship between the physico-chemical properties of the dispersions and their dissolution characteristics.

2. Materials and methods

2.1. Materials

PEG 6000 was purchased from Across Organics (New Jersey, USA). Pharmaceutical grade diazepam and temazepam were obtained from Federa (Brussels, Belgium) and Pharmacin (Zwijndrecht, the Netherlands), respectively. The water-content of the benzodiazepines was below 0.1% w/w. PEG 6000 flakes and dia crystals were ground with pestle and mortar. Ground PEG6000, ground dia and tem were passed through a 355-μm sieve. Solvents were of analytical or HPLC grade.

2.2. Methods

2.2.1. Gel permeation chromatography

Ten milligram PEG 6000 was dissolved in 10 ml mobile phase (0.01 M Na_2HPO_4, adjusted to pH 7 with 3 M H_3PO_4). The injection volume amounted to 100 μl and the column was a TSK G3000 PW, 60 cm × 7.5 mm (Tosohaas). The experiments were carried out at room temperature at a flow rate of 1 ml/min. PEG standards (molecular weight 620, 1080, 1900, 4120, 6450, 11 800, 22 800) were from Polymer Labs and the detection was performed with a refractive index detector. Mw and dp of PEG 6000 were found to be 6146 and 1.09, respectively.

2.2.2. Particle size analysis

Particle size analysis of dia and tem was carried out using a Coulter Multisizer II. The benzodiazepines were dispersed in 200 ml demineralized water, saturated in dia or tem, containing 0.9% w/

w NaCl and 0.01% w/w Tween 80. The dispersion media were filtered immediately before use through a nylon membrane filter with a pore size of 0.45 μm. The capillary tubes (orifice diameters 560 and 100 μm) were calibrated using latex spheres of different specific sizes. The particle size distribution was determined in a sample volume of 2 ml; experiments were performed in triplicate. The geometric mean volume diameters were found to be 22.32 and 14.07 μm for dia and tem, respectively.

2.2.3. Preparation of solid dispersions and physical mixtures

2.2.3.1. Physical mixtures. Physical mixtures, containing 5, 10, 20, 40% w/w of drug, were prepared by mixing accurately weighed amounts of dia or tem and PEG6000 in geometric proportions for 3 min with mortar and pestle. The physical mixtures were subsequently stored at room temperature in hermetically sealed glass bottles until use.

2.2.3.2. Solid dispersions prepared by the fusion method. Solid dispersions containing 0, 5, 10, 20 and 40% w/w of dia or tem were prepared by heating accurately weighed amounts of PEG6000 and drug in a closed teflon container in an oil bath at 80 °C. The mixtures were stirred repeatedly and after 10 min cooled either at room temperature or by placing the closed container for 15 min in a mixture of solid carbon dioxide and acetone (flash cooling). Subsequently, the solid dispersions were stored in vacuo over P_2O_5 for 72 h.

2.2.3.3. Solid dispersions prepared by the solvent evaporation method. Solid dispersions containing 0, 5, 10, 20 and 40% w/w of dia or tem were prepared by dissolving accurately weighed amounts of PEG6000 and drug in five parts of methylene chloride in a closed teflon receiver. After complete dissolution, the solvent was evaporated under reduced pressure at 35–40 °C in a rotovapor. Subsequently, the solid dispersions were stored in vacuo over P_2O_5 for 72 h.

All dispersions were pulverized with mortar and pestle, sieved (< 355 μm) and dried in vacuo over P_2O_5 for at least 48 h. All dispersions were stored at room temperature in hermetically sealed glass bottles until use.

2.2.4. Thermal analysis

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). Samples (2–6 mg) were weighed in aluminium pans (TA instruments, Brussels, Belgium), hermetically sealed and subsequently scanned at 1 °C/min under nitrogen gas purge (20 ml/min) (Verheyen et al., 2001). Indium and *n*-octadecane were used to calibrate and validate daily the DSC temperature scale; enthalpic response was calibrated and validated daily with indium. Data were treated mathematically using the PYRIS software version 3.6 (Perkin-Elmer).

In order to evaluate the presence of residual solvent in the solid dispersions prepared by the solvent evaporation method, samples (4–6 mg) were placed in open pans and heated under nitrogen purge (20 ml/min) from room temperature to 120 °C (dia) or 150 °C (tem) at 20 °C/min. Subsequently, the samples were kept isothermally during 3 min at these end temperatures, which are approximately 10 °C below the respective fusion temperatures of the pure drugs to avoid mass changes due to decomposition of the drugs during melting. Comparison of the masses before and after the assessment of the temperature programme, revealed that the mass loss was always less than 0.5%.

2.2.5. X-ray powder diffraction

2.2.5.1. Guinier camera method. Lattice spacings of PEG6000 were measured by X-ray powder diffraction using a Guinier camera XDC-700 (Stockholm, Sweden) equipped with a quartz crystal monochromator. A small sample in a rotating holder was exposed in vacuo and at room temperature to Cu Kα ($\lambda = 1.540598$ Å) radiation (40 kV × 20 mA) generated by a PW1720 X-ray generator (Philips, Eindhoven, The Netherlands). Silicon (SRM 640b) was used as an internal standard. The direct beam was held for 2 s at 10 kV and 5 mA. X-ray diffraction data were

recorded on a film (CEA, Reflex 15, Sweden) for 90 min. The positions and the intensities of non-overlapping lines of PEG6000 were evaluated by means of a computer-controlled microdensitometer for line pattern photographs (Line scanner LS-20 KEJ Instruments, Täby, Sweden).

2.2.5.2. Bragg-Brentano powder diffractometry. Powders were, without further grinding, placed in the sample holder by the top-loading technique. Diffraction patterns were obtained at room temperature on a Philips PW 1050 diffractometer (Philips) modified for step-scan operations. The Cu Kα radiation ($\lambda = 1.54184$ Å) was Ni filtered. Diverging and anti-scattering slits were set at 1°, the receiving slit at 0.2 mm. Tube voltage and tube current were 40 kV and 40 mA, respectively and the diffraction patterns were collected in the angular range $5° < 2\theta < 60°$ in step scan mode (step interval 0.02°, counting time 1s/step). The degree of crystallinity of the drug in a solid dispersion was estimated by comparing the ratio of the intensity of a non-overlapping diffraction line of a benzodiazepine and the intensity of a non-overlapping line of PEG in a solid dispersion with the ratio of the intensities of those lines in the corresponding physical mixture.

2.2.6. Infrared spectroscopy

KBr pellets were prepared by gently mixing 1 mg powder (PEG6000, drug, physical mixture or solid dispersion) with 200 mg KBr. Fourier transform-infrared spectra (500–4000 cm^{-1}) were obtained on a Perkin Elmer 2000 FT-IR apparatus (Perkin-Elmer) with a resolution of 2 cm^{-1}.

2.2.7. Solubility measurements and determination of thermodynamic parameters

The solubility of dia and tem in demineralized water and in mixtures of demineralized water and PEG6000 (1, 5, 10, 15% w/w) was determined by adding an excess of drug to 10 ml demineralized water or PEG6000 solutions in glass tubes. The stoppered tubes were rotated for 96 h in water baths at 30 ± 0.5 and at 40 ± 0.5 °C. Preliminary experiments had shown that this time period was sufficient to assure saturation. After equilibrium had been attained, the saturated solutions were immediately and rapidly filtered through a 0.20 μm membrane filter and diluted with water to prevent crystallisation. All material used for the filtration was brought to the same temperature as the solutions. Each experiment was performed in triplicate and the filtered and diluted solutions were analysed for dia or tem by HPLC. The heats of solution (ΔH in J/mol) were calculated from the slopes of the Van't Hoff plots using following equation:

$$\ln S_s = -\Delta H(RT)^{-1} + C$$

The Gibbs free energy changes (ΔG in J/mol) at 30 and 40 °C were calculated using the following equation:

$$\Delta G = -RT \ln(S_s S_w^{-1})$$

S_s is the solubility (mol/l) of the drug in water or PEG solution, R the gas constant (8.3143 J/K/mol) T the temperature (K), C a constant and $(S_s S_w^{-1})$ the ratio of the molar solubility of the drug in water or PEG solution to the molar solubility of the drug in water.

2.2.8. Dissolution studies

Dissolution studies were carried out using the paddle method (paddle speed 50 rpm) (USP XXIV). Samples of drug, solid dispersions and physical mixtures equivalent with 10 mg drug were clamped between infusion filter paper (Bollore Technologies, France), in order to prevent them from floating on the surface of the dissolution medium, and immersed in the dissolution medium (1000 ml ultrapure water at 37 °C). At designated time intervals, 1 ml samples were withdrawn, filtered (0.20 μm), analyzed by HPLC and replaced by the same amount of fresh dissolution medium. The dissolution experiments were performed in triplicate.

2.2.9. HPLC-analysis of diazepam and temazepam

Concentrations of dia and tem were determined using an isocratic HPLC method on a system equipped with a L-7100 Lachrom pump, a L-7400 Lachrom UV-detector, a L-7200 Lachrom autosampler and a D-7000 interface (all from Merck-Hitachi, Darmstadt, Germany). The column used was a LiChrospher 60 RP Select B (125×4 mm, 5

μm) (Merck, Darmstadt, Germany); the flow rate amounted to 1 ml/min and the volume injected 20 μl. The mobile phase consisted of acetonitrile and a phosphate buffer (pH 5.5; 0.05 M containing 0.03 M of triethylamine). The detector wavelength was set at 230 nm. The ratio of acetonitrile to buffer (v/v) was 45/55 for dia and 42/58 for tem. The relative standard deviations of the interday and intraday variabilities amounted to less than 3% ($n = 7$) and less than 2% ($n = 6$), respectively.

3. Results and discussion

The solubility of dia and tem was determined in demineralised water at 30 °C to be 0.055 and 0.130 g/l, respectively. The influence of the presence of PEG 6000 and the temperature upon the solubilities of dia and tem are presented in Fig. 1. The increase of the solubility with increasing PEG6000 concentration indicates the solvent properties of PEG6000 for both drugs. For example, at the highest PEG concentration (15% w/w) at 30 °C, the solubility of dia and tem increases approximately 3.5 and 2.5fold, respectively. The increase of the solubility with increasing temperature shows the endothermic nature of this process and suggests the absence of important hydrogen bond formation between drug and polymer since an increase in temperature disfavours hydrogen bonding.

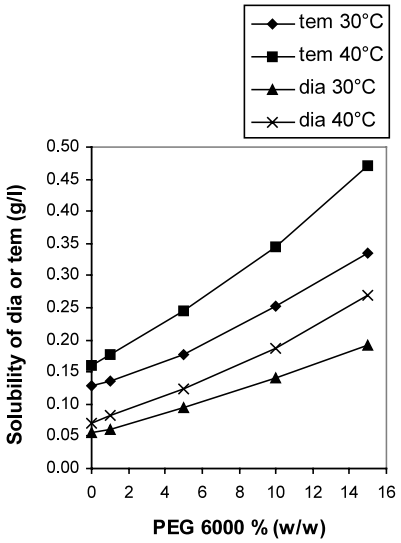

Fig. 1. Solubilities of tem and dia at 30 and 40 °C in PEG6000 solutions.

The thermodynamic parameters of the solubility process are given in Tables 1 and 2. The negative nature of the Gibbs free energy changes are indicative of the spontaneity of the process. The endothermic heats of solution further explain the increase in solubility with temperature. The endothermic nature of the heats of solution, the fact that an increase in temperature does hardly affect the changes of entropy and the clear similarities in thermodynamic parameters between dia and tem tend to rule out hydrogen bonding between the hydroxyl function of tem and an ether function of the polymer (Al-Angary et al., 1996).

In order to evaluate possible solid solution formation between the drugs and PEG, the lattice spacings of PEG6000 in different solid dispersions were determined. The effect of dia on some lattice spacings of PEG6000 is shown in Table 3. A systematic change in cell parameters of PEG6000 will result in a gradual shift in the positions of the diffraction lines of the polymer and can be considered as an indication of solid solution formation (Damian et al., 2000). The variations shown in Table 3 as well as those determined for solid dispersions containing tem are within three times the standard deviations proposed for Guinier measurements (Use of the Powder Diffraction File, PA, USA), providing evidence for the absence of interstitial or substitutional solid solution formation.

The diffraction spectra of diazepam, temazepam and PEG6000 show numerous distinct lines indicating that they are present in a highly crystalline state (Figs. 2 and 3). The spectra of PEG6000, treated by either the solvent evaporation method or the fusion method (slow or fast cooled) are identical. All solid dispersions show diffraction lines corresponding with those of pure drug, indicating that the solid solubility of the two benzodiazepines under investigation in PEG6000 is less than 5% w/w and moreover; this suggests the absence of formation of polymorphic crystal forms of the benzodiazepines during solid dispersion preparation. Indeed, since during solid dispersion

Table 1
Thermodynamic parameters of the solubility process of dia in water-PEG6000

PEG (% w/w)	ΔH (kJ/mole)	ΔG (J/mole)		ΔS (J/K/mole)	
		30 °C	40 °C	30 °C	40 °C
0	20.72				
1	21.82	−312	−360	73.02	70.84
5	20.49	−1413	−1454	72.26	70.09
10	22.66	−2387	−2529	82.62	80.44
15	26.08	−3179	−3460	96.53	94.34

preparation, dia and tem were brought into the liquid state and subsequently recrystallised in the presence of PEG, formation of polymorphs or solvates of dia and tem is not unlikely to occur. Comparison of the ratios of the intensities of non-overlapping drug and PEG6000 lines in the solid dispersions with the ratios of the intensities of these lines in the corresponding physical mixtures, reveals that the crystallinity of the drug, whether dia or tem, in the solid dispersions is reduced. This reduction in crystallinity appears in all solid dispersions independent of the solid dispersion preparation method used.

In order to study possible interaction between PEG6000 and the benzodiazepines in the solid state, FT-infrared spectra were recorded. From the chemical structures, hydrogen bonding could be expected between the hydroxyl groups of PEG and the carbonyl functions of tem and dia and also between the hydroxyl group of tem and the ether oxygens of PEG6000. These interactions would result in peak broadening and a bathochromic shift of the absorption bands of the interacting functional groups. Absorption bands of functional groups of dia and tem possibly involved in a hydrogen bonding interaction with the polymer are γC=O and νC=O at 660 and 1687 cm^{-1}, respectively, for dia and γC=O, νC–OH, νC=O at 648, 1115 cm^{-1} and 1670 and 1691 cm^{-1} (fermi doublet), respectively, for tem (Neville and Shurvell, 1990; Neville et al., 1992). Comparing the spectra of physical mixtures with those of solid dispersions prepared by the solvent evaporation method or fusion method (slow, fast cooling), revealed no differences in the positions of the absorption bands, hence providing evidence for the absence of hydrogen bonding interactions in the solid state between PEG6000 and the benzodiazepines under investigation (Fig. 4).

PEG6000 crystallises forming lamellae with chains either fully extended (0) or folded once (1) or twice (2) (Buckley and Kovacs, 1975, 1976). The twice folded modification has a lower melting temperature with respect to that of the once folded; the melting temperature of the once folded modification is lower with respect to that of the extended form. The polymorphic modifications of PEG6000, can be qualitatively and quantitatively

Table 2
Thermodynamic parameters of the solubility process of tem in water-PEG6000

PEG (% w/w)	ΔH (kJ/mole)	ΔG (J/mole)		ΔS (J/K/mole)	
		30 °C	40 °C	30 °C	40 °C
0	16.86				
1	20.91	−122	−260	69.39	67.62
5	24.99	−805	−1099	85.08	83.30
10	24.93	−1673	−1994	87.76	85.98
15	26.90	−2397	−2807	96.64	94.86

Table 3
Lattice spacings of pure PEG6000 or solid dispersions with dia, prepared by the solvent method (CH_2Cl_2), the fusion method with fast cooling (CO_2) or with slow cooling (rT)

	2θ				
	14.636	15.112	19.153	22.046	26.206
PEG CH_2Cl_2	6.0530	5.8671	4.6356	4.0324	3.4016
5% dia CH_2Cl_2	6.0522	5.8702	4.6366	4.0303	3.3977
10% dia CH_2Cl_2	6.0452	5.8606	4.6315	4.0272	3.3945
PEG CO_2	6.0498	5.8590	4.6301	4.0293	3.3951
5% dia CO_2	6.0280	5.8733	4.6301	4.0307	3.3986
10% dia CO_2	6.0625	5.8644	4.6334	4.0236	3.4015
PEG rT	6.0473	5.8579	4.6301	4.0285	3.3977
5% dia rT	6.0663	5.8687	4.6373	4.0309	3.4000
10% dia rT	6.0535	5.8706	4.6358	4.0290	3.3999

Units are in Angström (Å).

evaluated by a high resolution DSC-method reported recently (Verheyen et al., 2001). It was shown that PEG6000 crystallises in the twice and once folded modification, when prepared by the solvent method, but it crystallises in the twice, once folded and extended modification, when

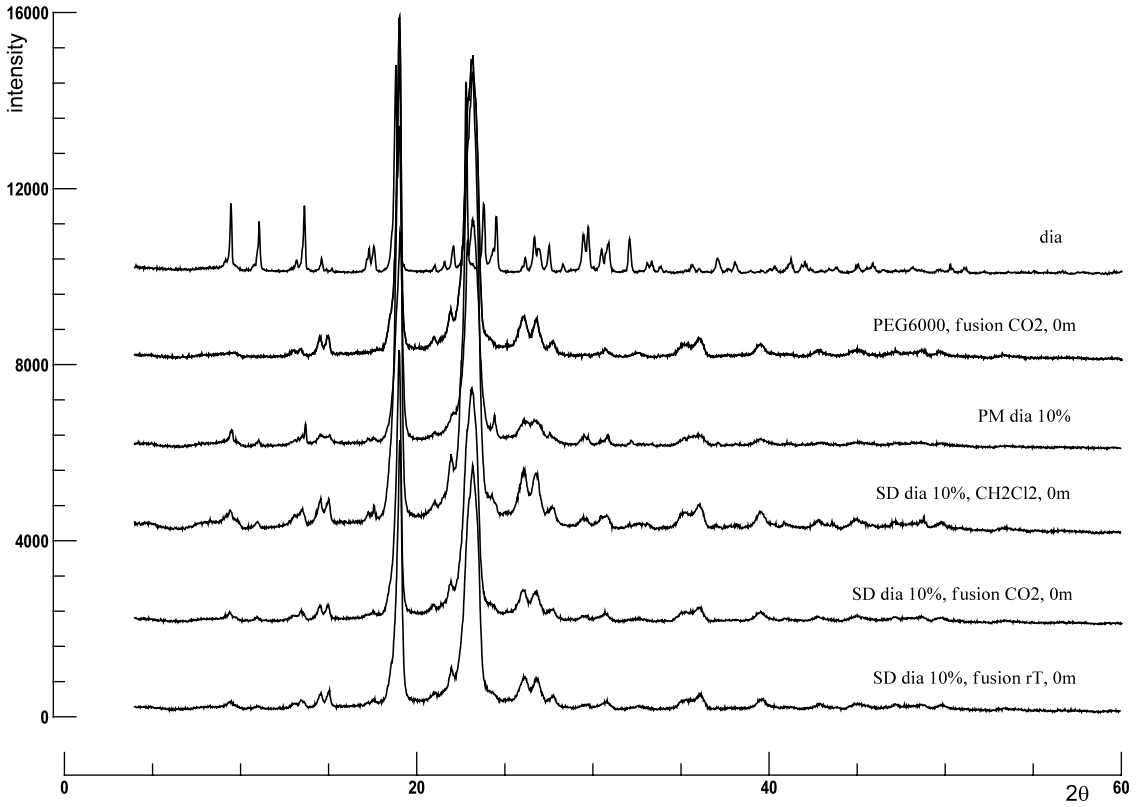

Fig. 2. X-ray diffraction patterns of dia, PEG6000, physical mixture (PM) and solid dispersions.

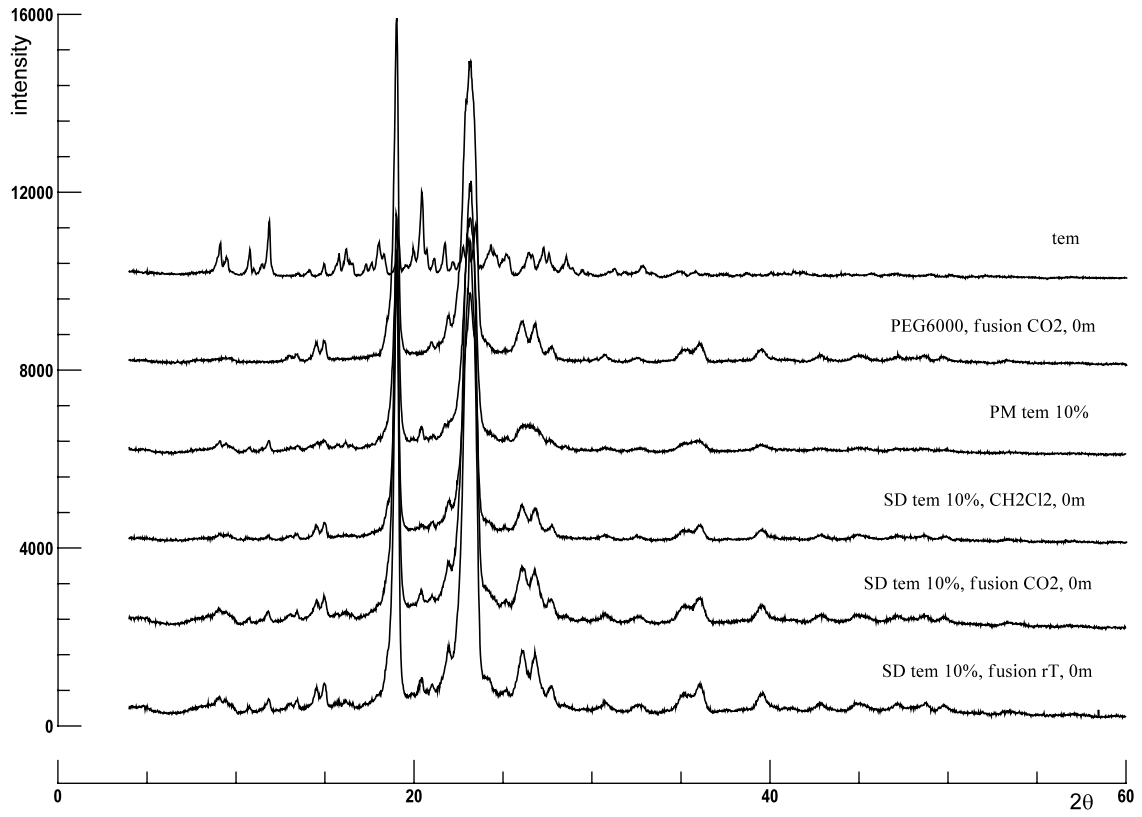

Fig. 3. X-ray diffraction patterns of tem, PEG6000, physical mixture (PM) and solid dispersions.

prepared by the fusion method. The DSC-curves of solid dispersions containing diazepam or temazepam, demonstrate that the incorporation of dia or tem promotes the formation of the twice folded modification and disfavors the formation of the extended modification (Fig. 5). Melting temperatures and relative distributions of PEG6000 modifications, weight corrected total heats of fusion of PEG6000 in solid dispersions of diazepam and temazepam, prepared by the solvent and the fusion methods and discussion have been published previously (Verheyen et al., 2001). Furthermore, incorporation of dia or tem slightly influences the enthalpy of fusion of PEG6000 and slightly lowers the peak temperatures of its different polymorphic forms.

Figs. 6 and 7 show the dissolution profiles of pure (100%) dia and tem and those of the different physical mixtures. Co-habitation of PEG6000 with the benzodiazepines clearly improves the dissolution rate of the last and the increase in dissolution rate is proportional with the PEG6000/drug ratio. The influence of PEG6000 on the dissolution of the benzodiazepines can be explained by the formation of regions of high concentration of dissolved polymer at the surface of drug crystals in which the drug can solubilise and subsequently diffuse and dilute in the bulk of the solution. Indeed, the fact that dia and tem show increased solubility in PEG6000 solutions with increasing PEG6000 concentration, as revealed by the solubility experiments, makes the above mechanism acceptable.

Figs. 8 and 9 show dissolution profiles of solid dispersions and the influence of the preparation method used upon these dissolution profiles. The differences are small compared with the experimental standard deviations, suggesting a minor

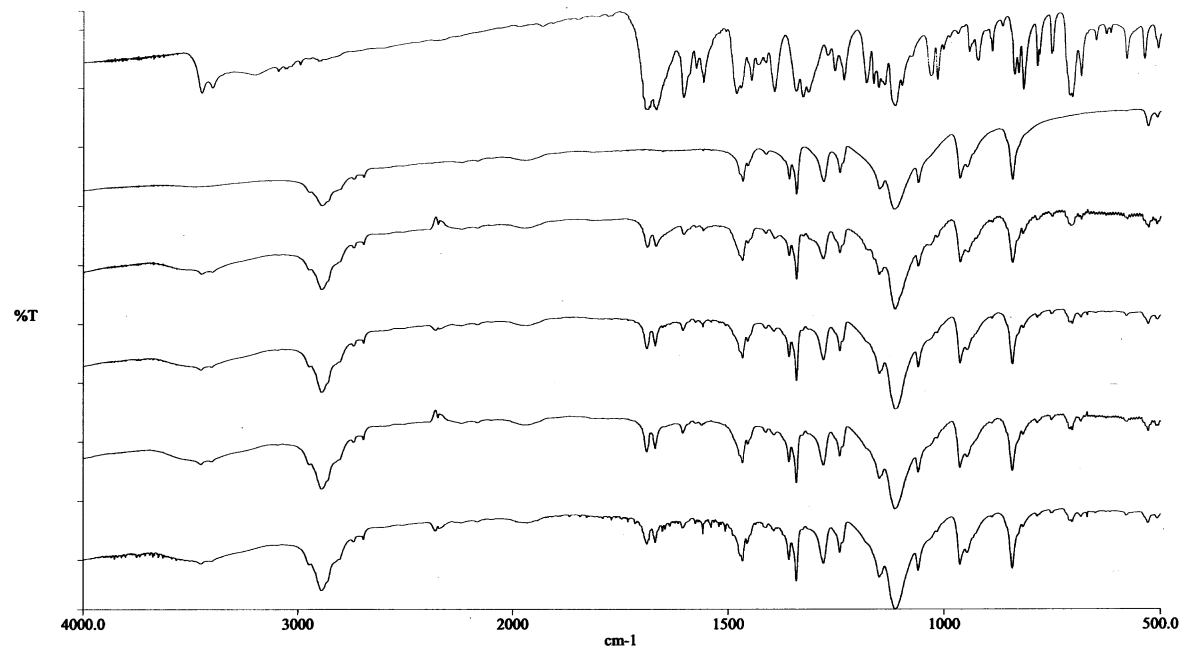

Fig. 4. FT-IR spectra of from top to bottom; tem, PEG6000 CH_2Cl_2, PM tem 10%, solid dispersions tem 10% CH_2Cl_2, tem 10% CO_2 and tem 10% rT.

influence of the preparation method used. Formulation of solid dispersions could theoretically further improve the dissolution compared with physical mixtures by reducing the drug particle size, formation of drug–polymer solid solutions, transformation of the drug to the faster dissolving amorphous state and by a more intimate contact between the polymer and the drug. Powder X-ray diffraction (Guinier camera method) ruled out the presence of an interstitial or substitutional drug–polymer solid solution whereas the Bragg-Brentano diffraction method showed a reduced crystallinity of dia and tem in the solid dispersions compared with the physical mixtures. This reduced crystallinity can be attributed to the formation of less perfect crystals and/or an amorphous drug fraction, both well known for their increased dissolution behavior. However, the dissolution profiles of the solid dispersions are not superior to the dissolution profiles of the corresponding physical mixtures. The differences seen in the DSC-curves of PEG6000 in solid dispersions prepared by the different preparation methods are attributed to polymorphism of the polymer. Differences in the distribution of the once-, twice-folded and extended modifications, due to the preparation method, seem to have a minor influence on the dissolution of dia and tem incorporated in solid dispersions, since the drug release profiles of solid dispersions prepared by the different methods are comparable.

Samples of drug, solid dispersions and physical mixtures equivalent with 10 mg of drug were clamped between infusion filter paper, in order to prevent them from floating on the surface of the dissolution medium, and immersed in the dissolution medium. Clamping of the powder samples between filter paper means that in the case of physical mixtures PEG6000 will stay close to and dissolve in contact with the drug particles. This experimental setup offers the possibility to estimate indirectly the size of drug particles in a solid dispersion by comparing their dissolution profile with that of a physical mixture with the same drug content and known drug particle size. The estimate

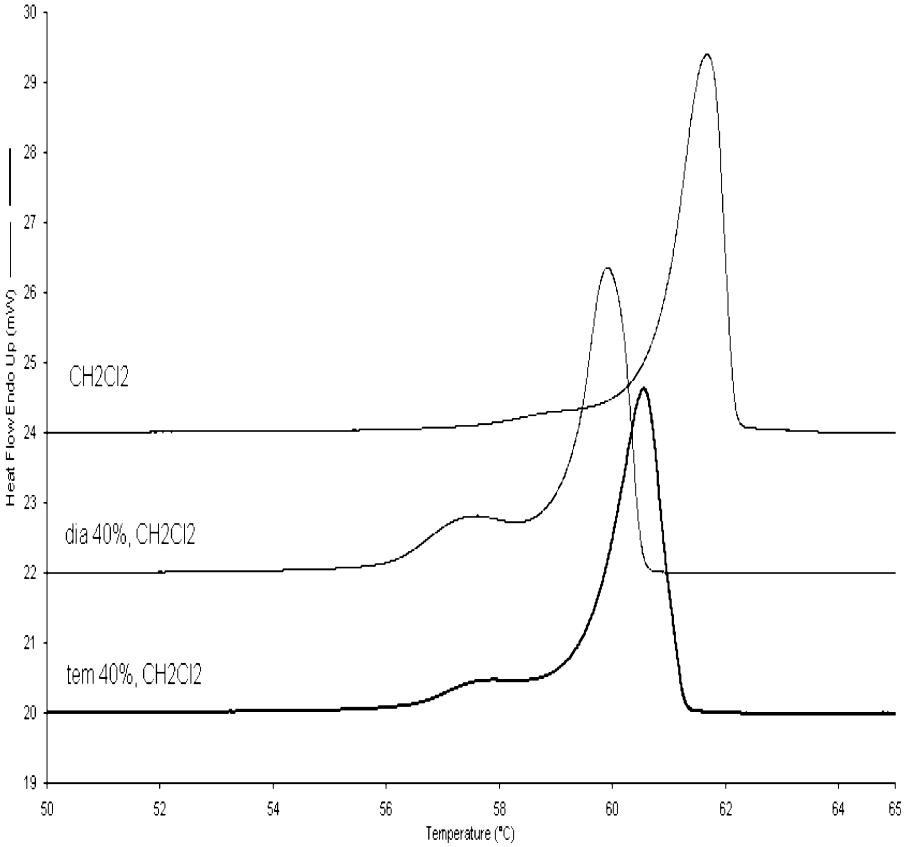

Fig. 5. DSC-curves of pure PEG6000 prepared by the solvent method and solid dispersions, prepared by the solvent method, containing 40% dia and 40% tem, respectively.

is of course rough, but most other techniques are not superior. For example, particle analysis by the Coulter principle (Sjökvist and Nyström, 1988; Sjökvist et al., 1989; Sheu et al., 1994) and all other methods with which the solid dispersion is dissolved in an aqueous medium, underestimate the number and size of the small drug particles because these small particles will rapidly dissolve in PEG-rich regions formed at the surface of the drug crystals in the dissolution medium, leaving the coarser particles to be analyzed. In the case of particle analysis by optical microscopy a very thin film of the solid dispersion is formed on a microscopy slide by slightly heating the solid dispersion, to reduce the viscosity of PEG6000, and placing a cover slide on top (Dordunoo et al., 1997). During this heating process, the smaller particles can dissolve in the polymer, leaving once again the coarser particles to be analyzed. The dissolution profiles of physical mixtures containing tem are clearly superior to those of the corresponding solid dispersions, suggesting that the particle size of tem in the solid dispersions is larger than that of the tem in the physical mixtures (geometric mean volume diameter of tem is 14.07 μm). The dissolution profiles of physical mixtures of dia and its corresponding solid dispersions show minor differences, suggesting that the particle size of the manually ground dia in the physical mixtures (geometric mean volume diameter of dia is 22.32 μm) is in the range of that of dia in the solid dispersions. These observations suggest that the mean particle size reduction of dia and tem by preparing solid dispersions with PEG6000 is limited and situated at a geometric mean volume diameter of approximately 20 μm.

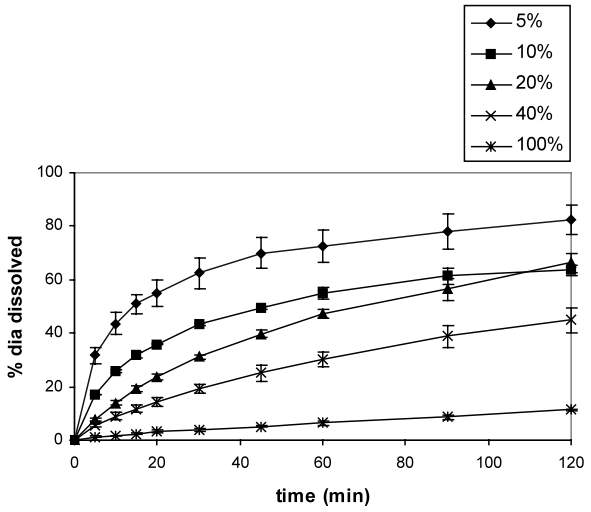

Fig. 6. Dissolution profiles of dia and physical mixtures with PEG6000. The percentages represent dia in PEG6000 by weight. Error bars indicate the standard deviations, $n = 3$.

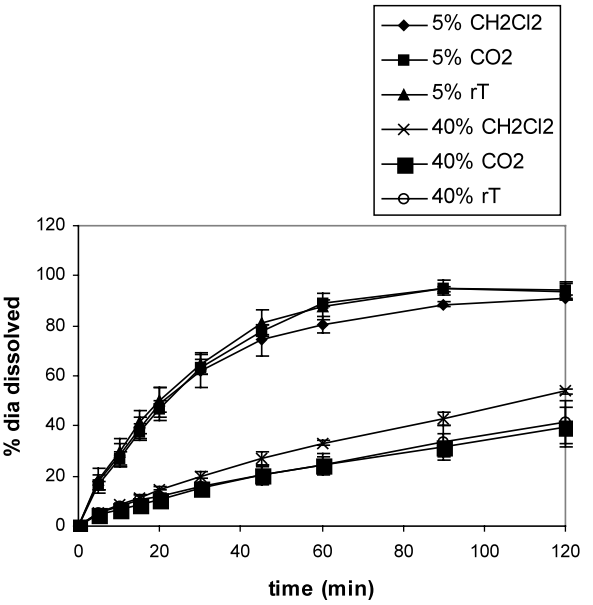

Fig. 8. Dissolution profiles of solid dispersions of dia with PEG6000, prepared by the solvent method (CH_2Cl_2), the fusion method with fast cooling (CO_2) or the fusion method with slow cooling (rT). The percentages represent dia in PEG6000 by weight. Error bars indicate the standard deviations, $n = 3$.

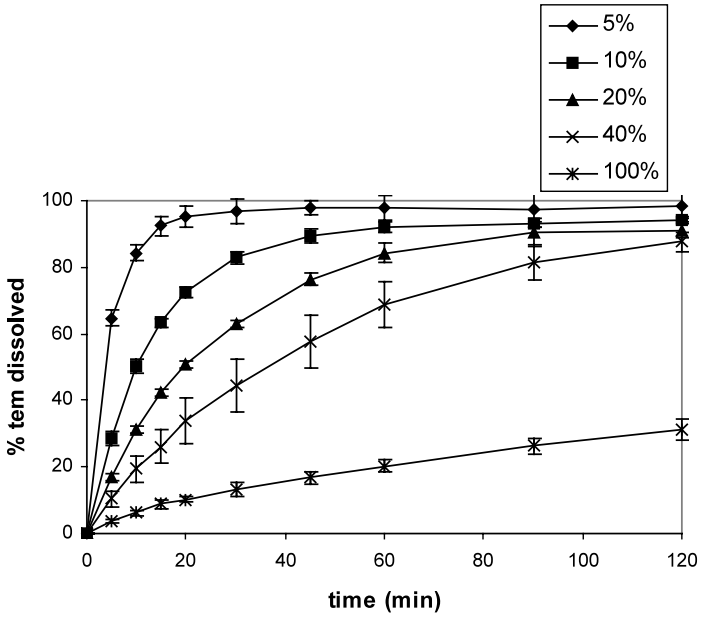

Fig. 7. Dissolution profiles of tem and physical mixtures with PEG6000. The percentages represent tem in PEG6000 by weight. Error bars indicate the standard deviations, $n = 3$.

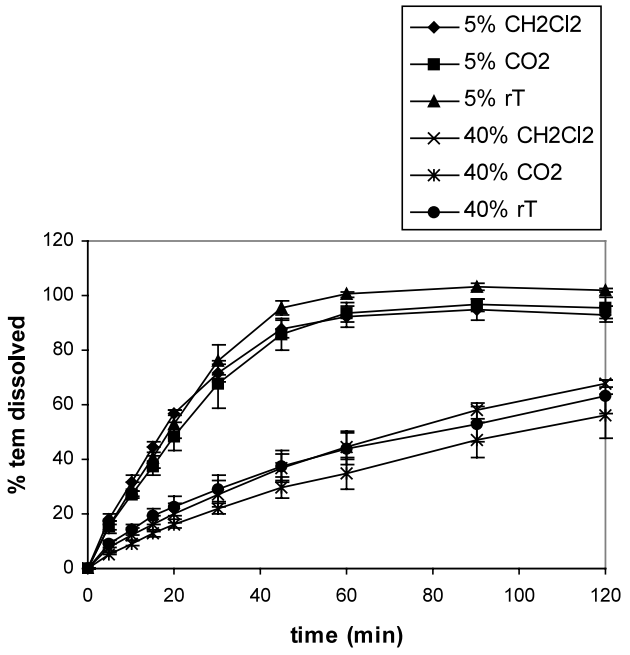

Fig. 9. Dissolution profiles of solid dispersions of tem with PEG6000, prepared by the solvent method (CH_2Cl_2), the fusion method with fast cooling (CO_2) or the fusion method with slow cooling (rT). The percentages represent tem in PEG6000 by weight. Error bars indicate the standard deviations, $n = 3$.

4. Conclusion

This study clearly shows that addition of PEG6000 to dia and tem improves their dissolution rates. Mechanisms involved are solubilisation and improved wetting of the drug in the polyethylene glycol rich micro-environment formed at the surface of drug crystals after dissolution of the polymer. Formulation of solid dispersions did not further improve the dissolution rate compared with physical mixtures. No solid solution formation and no hydrogen bonding interaction between PEG6000 and dia or tem could be detected. The crystallinity of both drugs was reduced in all solid dispersions, but this reduction did not result in any important dissolution improvement. Furthermore, it was concluded that the reduction of the mean drug particle size obtained by preparing solid dispersions with PEG6000 is limited and that the influence of the polymorphic behavior of PEG6000 (as observed by DSC) on the dissolution was negligible.

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