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GLASS FORMING PROPERTIES OF BENZODIAZEPINES AND CO-EVAPORATE SYSTEMS WITH POLY(HYDROXYETHYL METHACRYLATE)

G. Van den Mooter, J. Van den Brande, P. Augustijns and R. Kinget*

Laboratorium voor Farmacotechnologie en Bioformacie, Katholieke Universiteit Leuven
B-3000 Leuven, Belgium

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Abstract

In the present study, we report on the thermal properties of a series of benzodiazepines. The heat of fusion varied between approximately 25 and 40 kJ mol^{-1}, except for oxazepam and lorazepam where dimerization in the solid state increased the heat of fusion to 78.54(±0.37) and 77.03 (±0.84) kJ mol^{-1}, respectively. Heating alprazolam at a low rate (0.5 K min^{-1}) showed that polymorphs I and II are an enantiotropic pair with a solid-solid transition at 481.4 K It was shown that all benzodiazepines could be transformed to the glassy state by cooling fused samples, irrespective of the cooling rate.The size of the relaxation endotherm accompanying the glass transition increased by heating the glassy drugs at a higher rate through T_g or by cooling the fused samples at a slower rate. The time dependence of the glass to liquid transition can be described to a good approximation as a first order transformation. The Gordon-Taylor equation was used to predict T_g of a binary mixture of temazepam, diazepam or prazepam with polyHEMA. It was shown that the predictability was acceptable as long as the drug concentration was below 10%w/w; at higher concentration, specific drug-polymer interactions causing changes in free volume of the system could not be ignored.

Keywords: benzodiazepines, differential scanning calorimetry, glass transition temperature, solid dispersion

Introduction

It is generally recognized that the following four factors compromise the oral bioavailability of drugs from solid dosage forms: I) low solubility and/or dissolution rate in the gastro-intestinal (GI) tract, ii) low membrane permeability, iii) interaction with components of the GI tract leading to complex formation, and iv) metabolism in the liver, the GI lumen or in the GI mucosa (either membrane or cytosol related).

* Author for correspondence: tel.: 32-(0)16-345830, fax: 32-(0)16-345996, e-mail: guy.vandenmooter@farm.kuleuven.ac.be

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A possible pharmaceutical strategy that can result in increased solubility and dissolution rate is the use of solid dispersions. The term refers to a dispersion of one or more active ingredients in an inert and hydrophilic carrier or matrix in the solid state, prepared by melting (fusion) or solvent method. Solid dispersions are physicochemically classified as eutectics, solid solutions, glass solutions and suspensions, amorphous precipitates in a glassy or crystalline carrier, complex formations, and/or a combination of the different systems [1]. Although the use of solid dispersions has been reported frequently in the pharmaceutical literature, very few marketed products rely on the solid dispersion strategy [2]. The main reason for this discrepancy is the physical instability (aging effects) of these structures which are often metastable. Crystal growth or conversion from the amorphous (metastable) to the crystalline state during storage, inevitably results in decreased solubility and dissolution rate.

It is therefore of crucial importance to identify and understand the factors that influence crystal growth and crystallisation from the amorphous state. It has been shown by Yoshioka *et al.* [3] that indomethacin crystallises completely from the amorphous state at 30°C within several weeks while inhibition of crystallisation for periods longer than 6 months was only observed when the storage temperature was reduced to 4°C. The same authors demonstrated that a significant inhibition of crystallisation of indomethacin can be accomplished when the drug was coprecipitated with polyvinylpyrrolidon, which is a glassy polymer [4]. An important conclusion from this and other [5, 6] studies is that the glass transition temperature (T_g) dictates the conditions for optimal storage of an amorphous system (either the pure drug or a

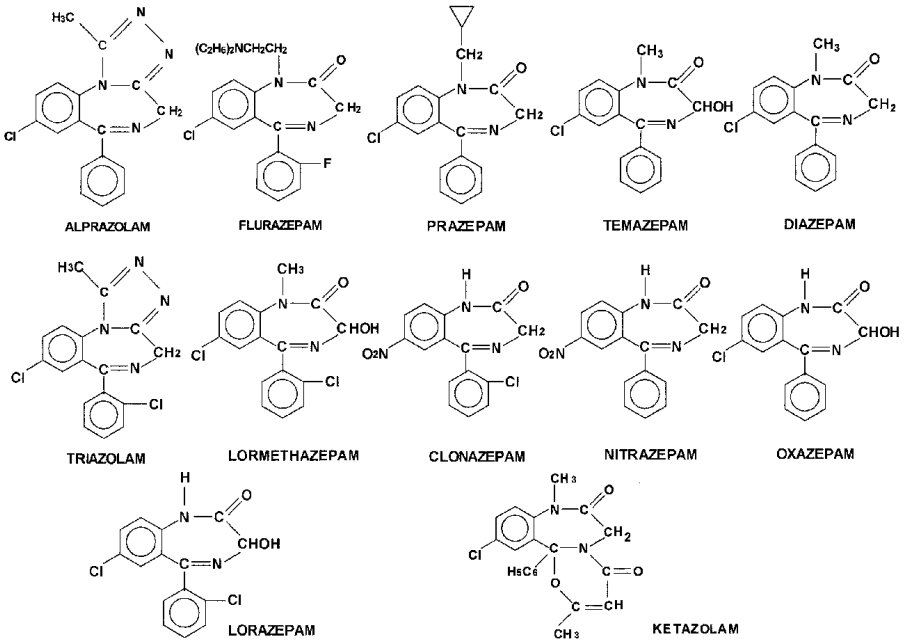

Fig. 1 Structural formulas of benzodiazepines

complex amorphous system), since it indicates the borderline between a region of low and high molecular mobility of the supercooled liquid state. Indeed, T_g is the point where relaxation to the equilibrium conformation, characteristic of the supercooled liquid at that particular temperature, is impaired [7, 8]. Therefore, a glass has a frozen-in molecular conformation typical of some higher temperature liquid.

In the present paper we report the first part of a study on the characterisation and glass formation properties of a series of benzodiazepines of which the structural formulas are given in Fig. 1. We also investigated the mixing behaviour of benzodiazepines with a model hydrophilic polymer, poly(hydroxyethyl methacrylate), by evaluating the quantitative relationship between the concentration of a particular benzodiazepine and T_g of a binary mixture of that particular benzodiazepine with the polymer.

Materials and methods

Materials

Temazepam was kindly donated by Sanico (Turnhout, Belgium), diazepam, nitrazepam and clonazepam by Roche (Basel, Switzerland), ketazolam and triazolam by Pharmacia and Upjohn (Puurs, Belgium), prazepam by Parke-Davis (Orléans, France), alprazolam by SMB (Brussels, Belgium) and flurazepam by Madaus Pharma (Brussels, Belgium). Oxazepam, lormetazepam and lorazepam were obtained from Asma-Borgers (Deurne, Belgium). 2-Hydroxyethyl methacrylate (HEMA), azobisisobutyronitrile (AIBN), and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) were obtained from Acros Chimica (Geel, Belgium).

Methanol and methylene chloride (both from Biosolve, the Netherlands) were purified by distillation.

Synthesis of polyhydroxyethyl methacrylate (poly HEMA)

500 ml of HMDS was added dropwise to 515 ml of HEMA in a three-necked round bottom flask. During the reaction, the mixture was purged with N_2 and cooled with ice. Following complete addition of HMDS, purgation was discontinued and the reaction mixture was left at room temperature for 12 h. Subsequently, the silylized HEMA was distilled under reduced pressure at 40°C and collected in an ice-cooled round-bottom flask. The silylized product was hydrolyzed with HCl and the aqueous layer was collected. From this mixture, HEMA was extracted with methylene chloride. This solution was dried over magnesium sulfate and evaporated under reduced pressure. The collected monomer was subjected to a second vacuum distillation.

^{1}H-NMR (CDCl3) analysis revealed pure HEMA (δ in ppm): δ=1.93 (CH_3, 3H); δ= 3.84 and 4.26 (–OCH_2CH_2O–, 4H); δ=4.80 (–OH, 1H); δ=5.75 and 6.29 (CH_2=C, 2H). The purified monomer was flushed with N_2 and stored at 4°C until polymerisation.

PolyHEMA was synthesized by adding 100 ml of 2-HEMA to 900 ml of methanol:methylene chloride (50:50; v/v) in which 1% (w/v) of AIBN (freshly recrystallized from methanol) was dissolved. The reaction mixture was heated at 60°C for 24 h, after which the polymer was precipitated in an excess of hexane and washed with water. This purification step was repeated twice. The polymer was dried at constant mass under reduced pressure at 60°C.

Determination of M_w, M_n, and polydispersity (*dp*) was achieved using gel permeation chromatography. Approximately 50 mg of polyHEMA was dissolved in l0 ml of a mixture of dimethylsulfoxide and tetrahydrofuran (50:50; v/v). 100 µl was injected into a Mixed B column (Polymer Lab) at 40°C. The flow rate was 1 ml min^{-1} and detection was carried out using refractive index. Calibration was performed with polystyrene standards of known molecular mass. The values obtained for polyHEMA were $M_w=37.7\cdot10^3$; $M_n=30.9\cdot10^3$; *dp*=1.22.

Preparation of binary solid dispersions

Co-evaporated systems of temazepam, prazepam and diazepam were prepared by dissolving the drug and polyHEMA in a minimum amount of distilled methanol. The solvent was rapidly removed by evaporation under reduced pressure at 40°C. The dispersions were stored in a dessicator for 24 h, ground in a mortar, passed through a 350 µm sieve, and stored in a dessicator until use. Physical mixtures of temazepam, diazepam and prazepam with polyHEMA were prepared by trituration during 3 min in a mortar until a homogeneous mixture was obtained. The mixture was passed through a 350 µm sieve and stored in a dessicator until use.

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, USA). Samples (2–6 mg) were weighed and analyzed in closed aluminum pans. In order to determine the heat of fusion (ΔH_f) of pure benzodiazepines, the samples were heated at 20 K min^{-1} to 40 K below their melting point (T_m), and subsequently scanned at 5 K min^{-1}.

T_g of the pure drugs was determined by heating them at l0 K min^{-1} to T_m+10 K, followed by quench cooling to 268.15 K (in the case of flurazepam the samples were cooled to 253.15 K) and subsequent rescanning at 3 K min^{-1}. In order to evaluate the enthalpy recovery and the temperature dependence of T_g, fused samples were cooled from T_m+10 K to T_g–30 K at a rate of 3, 10 or 20K min^{-1}, and rescanned through their T_g at 3, 10 or 20 K min^{-1}.

Co-evaporates and physical mixtures were scanned from 293.15 to 403.15 K at 5 K min^{-1}. Temperature calibration was performed using pure water and indium for each scanning rate; enthalpic response was calibrated with indium and afterwards validated using decane and zinc. Data were treated mathematically using the Pyris Software (Perkin Elmer, Norwalk, CT, USA).

Density measurements

Density of temazepam, diazepam, prazepam and polyHEMA was determined using a Beckman model 930 Air Comparison Pycnometer (Beckman Instruments, Inc., USA).

Results and discussion

Table 1 shows the melting points (T_m) and the corresponding heat of fusion (ΔH_f) as well as the glass transition temperature (T_g) of the various benzodiazepines. T_g values reported in Table 1 were obtained by quench cooling fused samples followed by reheating at 3 K min^{-1}. Except for alprazolam, all molecules showed one single melting point. When alprazolam was heated at a rate of 5 K min^{-1} two endotherms at 495.7 and 502.1 K, and one exotherm between them could be observed, indicating that this drug exists in two polymorphic forms. The endotherm at 502.1 K was a melting endotherm of polymorph II and this was confirmed with hot-stage microscopy. The endotherm at 495.7 K was confirmed with hot-stage microscopy to be the melting transition of polymorph I, the exotherm following this endotherm indicates a crystallisation of the melt to form a solid phase. It has been shown by Laihanen and Yliruusi [9] that the first endotherm disappeared when the sample was heated at a lower heating rate (1 K min^{-1}). However, these authors did not give an explanation for the observed phenomena. When we varied the heating rate (5 gradually to 0.3 K min^{-1}), we observed that the heat of fusion of I decreased with decreasing heating rate, while the heat of fusion of II remained unchanged. Moreover, heating below 1 K min^{-1} led to a complete disappearance of the endotherm at 495.7, instead a new endotherm at 481.4 K appeared, which could be attributed to a solid-solid transition; the endotherm at 502.1 K remained unchanged (Fig. 2). The solid-solid transition suggested that pure polymorph II can be formed by heating alprazolam somewhat below 495.7 K, which we were able to confirm in additional experiments. The same observations were made by Behme *et al.* [10] for gepirone hydrochloride.

ΔH_f is a measure for the energy (work) which has to be supplied to transfer a crystal to the liquid state. In the series of benzodiazepines studied, the heat of fusion ranges from approximately 25 to 78 kJ mol^{-1}, indicating that the lattice energy varies significantly between these structurally related molecules. The highest values were observed for oxazepam and lorazepam: the experimental values of ΔH_f for oxazepam and lorazepam are 78.6 and 77.0 kJ mol^{-1}, respectively, which is almost twice as those of the other benzodiazepines studied. Taking a closer look at the structural formulas, it is clear that both molecules lack a substituent on the N1 atom of the diazepine ring and the possibility exists for hydrogen bonding between the hydrogen on N1 and the oxygen atom of the carbonyl group of an adjacent molecule to form a dimer in the solid state. However, the same situation exists for nitrazepam and clonazepam, but the heat of fusion of these molecules is only 31.9 and 35.5 kJ mol^{-1}, respectively, and thus hydrogen bonding between –NH and the oxygen of the carbonyl group of an adjacent molecule can probably not completely explain the higher

heat of fusion of oxazepam and lorazepam. However, both molecules also bear a hydroxyl function at position C_3 of the diazepine ring, which on its turn can form a dimer by hydrogen bonding between the hydroxyl and the oxygen of the carbonyl on an adjacent molecule. Thus, at least theoretically, oxazepam and lorazepam have double possibilities to form dimers as compared to nitrazepam and clonazepam, and

Table 1 Thermal properties of the benzodiazepines

Drug	T_m/K	ΔH_f/kJ mol^{-1}	T_g/K	T_m/T_g
Flurazepam	352.8	33.93	271.9	1.29
	(±0.3)	(±0.16)	(±0.1)	
Prazepam	418.8	27.82	303.4	1.38
	(±0.1)	(±0.05)	(±0.7)	
Temazepam	432.6	27.40	339.2**	1.27
	(±0.1)	(±0.90)	(±1.6)	
Diazepam	404.5	25.78	315.2	1.28
	(±0.1)	(±0.19)	(±0.4)	
Triazolam	513.8	40.56	356.5	1.44
	(±0.1)	(±0.54)	(±0.3)	
Alprazolam	495.7 (I)	‡ (I)	364.7	1.38
	(±0.0)	(±1.89)	(±0.2)	
	502.1 (II)	29.05 (II)		
	(±0.1)	(±1.88)		
Lormetazepam	483.5	36.52	336.7	*
	(±0.2)	(±0.25)	(±0.6)	
Clonazepam	512.5	35.47	361.6	*
	(±0.1)	(±1.07)	(±0.6)	
Nitrazepam	501.1	31.89	363.7	*
	(±0.1)	(±0.93)	(±0.1)	
Oxazepam	470.4	78.54	291.2	*
	(±0.2)	(±0.37)	(±0.9)	
Lorazepam	450.1	77.03	295.5	*
	(±0.6)	(±0.84)	(±1.4)	
Ketazolam	452.7	32.76	291.7	*
	(±0.2)	(±0.82)	(±2.7)	

* not determined due to coloration of the melted samples.

Data between parenthesis indicate standard deviation; n=3

** Dordunoo *et al*. [22] reported a value of 443 K (scaning rate was 10 K min^{-1}).

‡ the value for polymorph I was dependent on the heating rate, and is therefore not reported.

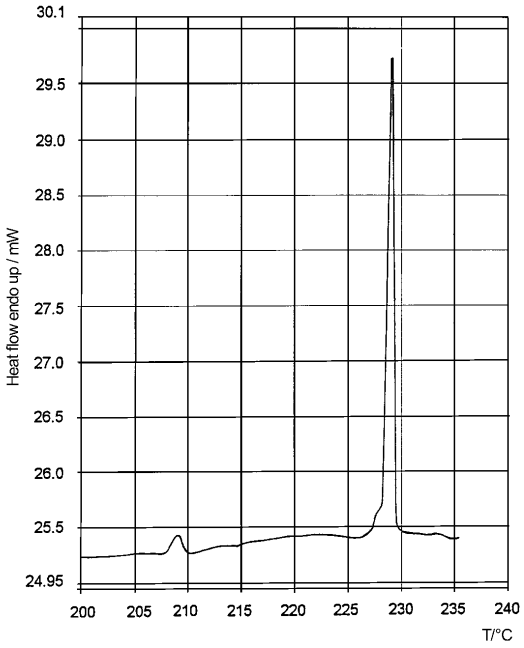

Fig. 2 DSC curve of alprazolam; heating rate: 0.5 K min^{-1}

this may explain their higher heat of fusion. Evidence for the existence of dimers in oxazepam, lorazepam, nitrazepam, and clonazepam in the solid state was reported by Neville *et al.* [11, 12] using vibrational spectroscopy. Surprisingly, these authors could not demonstrate hydrogen bonding in temazepam and lormetazepam, although theoretically dimerisation can occur.

In the present study we wanted to investigate the possibility of glass formation in a series of benzodiazepines. The amorphous state may be of interest to the pharmaceutical scientist since due to its higher internal energy and specific volume, it can result in enhanced solubility and dissolution as compared to the crystalline state. Many drugs do not immediately crystallize when they are cooled through their melting point, but they form a supercooled liquid instead [8, 13–15]. Further cooling leads to such high viscosities that molecular mobility is impaired, thereby inhibiting further recrystallisation, and the possibility exists that this supercooled liquid becomes an immobile glass with a frozen-in molecular conformation, typical of some higher temperature supercooled liquid. In order to determine the glass transition temperature (T_g), the benzodiazepines were quench-cooled from T_m+10 K to 268.15 K, except for flurazepam which was cooled to 253.15 K, and subsequently heated at 3 K min^{-1}. During reheating, oxazepam, lorazepam and alprazolam showed a recrystallisation exotherm at 349.5(±4.9), 372.2(±1.0) and 428.1(±2.0) K, respectively. In the case of alprazolam, crystal modification II was formed upon re-

crystallisation, while in the case of lorazepam and oxazepam, other products were formed, probably degradation products since after recrystallisation, endotherms were observed which did not correspond to T_m of the pure compounds. Moreover, monitoring the melting process of all benzodiazepines with a hot stage microscope revealed a change of colour at T_m for oxazepam, lorazepam, lormetazepam, ketazolam, nitrazepam, and clonazepam, and therefore, the reported value of T_g for these compounds may not represent T_g of the pure drugs, but instead that of a degradation product or a mixture of degradation products in case of oxazepam and lorazepam. This indicates that solid dispersions of these drugs should be monitored carefully with respect to degradants when they are produced by a fusion method. Preferably, solid dispersions of these drugs are prepared using the solvent method, thus avoiding high processing temperatures.

Super-cooled liquids can be classified as either 'strong' or 'fragile' systems [16]. The term 'fragility' refers to some kind of measure of the temperature dependence of molecular motions in the glass transition region. The importance of 'fragility' lies in its relationship to physical and chemical stability of materials as a function of temperature. Open network liquids (e.g. SiO_2) show Arrhenius variation of the structural relaxation time with temperature and are classified as strong liquids, while the viscosities vary in a non-Arrhenius like manner with temperature in fragile liquids. When relaxation time data are not available, the ratio T_m/T_g can be used as a rule of thumb to classify amorphous systems: for strong liquids, $T_m/T_g > 1.5$, while $T_m/T_g < 1.5$ for fragile liquids. From the values reported in Table 1, it is clear that the six ben-

Table 2 Relaxation enthalpies at T_g of benzodiazepines at different heating and cooling rates

Drug	ΔH_f/J mol^{-1}					
	Heating/cooling rate/K min^{-1}					
	Q/3	3/3	10/3	20/3	20/10	20/20
Flurazepam	65.5	154.4	89.2	69.0	212.6	254.8
	(±1.9)	(±8.5)	(±22.9)	(±10.1)	(±16.7)	(±61.3)
Prazepam	100.5	206.27	167.6	119.2	218.6	334.9
	(±34.1)	(±18.8)	(±26.9)	(±22.4)	(±33.4)	(±10.1)
Temazepam	103.4	295.6	200.15	144.7	231.3	413.2
	(±23.2)	(±64.9)	(±26.2)	(±41.5)	(±13.5)	(±6.3)
Diazepam	132.4	255.7	195.7	156.3	210.7	305.8
	(±19.9)	(±19.4)	(±38.2)	(±4.6)	(±17.1)	(±15.7)
Triazolam	82.4	215.2	186.7	164.1	241.6	351.5
	(±26.1)	(±135.2)	(±34.2)	(±54.9)	(±15.8)	(±34.0)
Alprazolam	137.7	220.8	175.7	170.4	284.9	319.6
	(±37.7)	(±68.6)	(±31.2)	(±58.7)	(±4.9)	(±44.5)

Q=quech cooling

zodiazepines can be classified as fragile amorphous systems. Similar values were reported for indomethacin (1.37) and sucrose (1.29) [17], while Summers [15] reported values between 1.33 and 1.68 for a series of barbiturates.

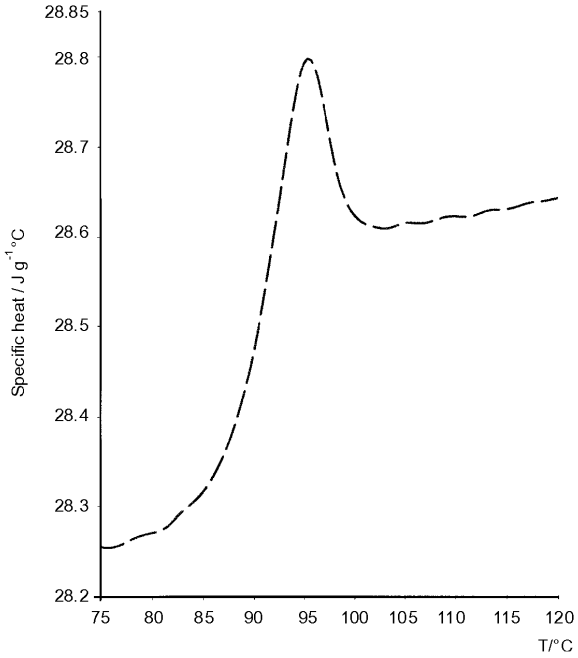

Fig. 3 DSC curve showing the glass transition of triazolam. Conditions: cooling from the melt at 20 K min^{-1} to T_g–30 K, followed by heating at 20 K min^{-1}

In order to further characterize the glass forming properties of benzodiazepines, we investigated the influence of cooling and heating rate on the thermal behaviour. The results are shown in Table 2. A jump in heat capacity as shown in Fig. 3 for triazolam was observed for all benzodiazepines under all conditions indicating that, irrespective of the cooling rate, a glass was formed. Following quench cooling of the melted molecules (T_m+10 K), a small endothermic relaxation peak at T_g was observed. However, when the melts were cooled at a lower rate, the size of the endotherm increased. This can probably be explained by assuming that during cooling, annealing already occurs, during which the system is able to relax to the equilibrium state. Increasing the scanning rate from 3 to 20 K min^{-1}, also led to an increase of the enthalpic relaxation endotherm, which can also be explained by recovering enthalpy of relaxation during heating. The heat capacity may be considered to have a vibrational component for the glassy and additionally a relaxational component for the liquid state. When temperature decreases to a value well above T_g, the relaxational and vibrational enthalpy decrease instantaneously. In the T_g region, however, molecular mobility falls and a finite time is required for the relaxational enthalpy to at-

tain its equilibrium value, and relaxation times varying from fractions of seconds to infinity have been encountered when passing through the T_g region [7].

Barton [18] considered the glass transition to be a first order process with the rate of transformation from a glass to a liquid when heating through T_g being

$$\ln\left(\frac{n_o}{n}\right) = \frac{1}{F}\int k\,dt \tag{1}$$

where n_o and n are the mole fractions of glass molecules at time zero and t, respectively, F is the heating rate, T is the temperature, and k is the rate constant. From Eq. (1), the following equation is derived:

$$\log\frac{F}{T^2} = C - \frac{E}{2.303RT} \tag{2}$$

When assuming that $\log T^2$ is constant [18], the equation can be written as follows:

$$\log F = C/ - \frac{E}{2.303RT} \tag{3}$$

where C' is a constant, T is the apparent T_g and E is the activation energy. In this approach, T_g is defined as the temperature corresponding to any fixed fractional degree of transformation. The dependence of the apparent T_g on the heating rate was investigated by scanning melts which were cooled at 20 K min^{-1} to T_g–30 K. Figure 4 shows a plot of log$F$ *vs.* T_g^{-1}. Using least square analysis, the following values for the activation energy (in kJ mol^{-1}) were obtained: 204.5 for flurazepam, 243.6 for prazepam, 304.3 for temazepam, 221.2 for diazepam, 295.8 for triazolam, and 278.3 for alprazolam. Taking into account that the value of the linear regression slope is highly sensitive to experimental error, it can be concluded that the obtained values

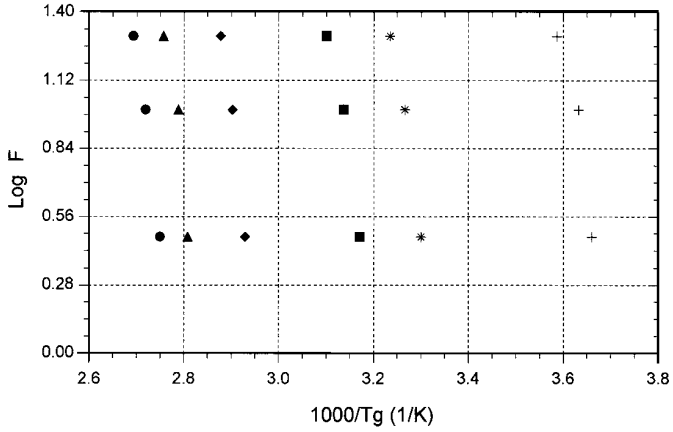

Fig. 4 Plots of log$F$ *vs.* $10^3/T_g$ for temazepam (◆), prazepam (*), diazepam (■), triazolam (▲), alprazolam (●), and flurazepam (+). LogF= C'–E/2.303RT, where C' is a constant, T is the apparent T_g and E is the activation energy

are comparable, and the linear behaviour of log$F$ *vs.* T_g^{-1} ($0.96<r<0.99$) indicates that the time dependence of the transformation of the benzodiazepines from the glassy to the liquid state can be treated to a good approximation as a simple first order conversion.

In order to investigate the behaviour of benzodiazepines in binary solid dispersions with a model hydrophilic polymer containing two possible sites for interaction, we studied the variation of T_g of the blend as a function of its composition. It is well established that T_g of a compatible mixture varies between T_g values of the pure components, and therefore, the use of a component with a higher T_g than that of the drug offers the possibility to increase T_g above that of the drug. T_g of the blend dictates the storage temperature which must be well below T_g of the blend in order to prevent recrystallisation of the drug from the amorphous state. One single glass transition was observed in the three types of mixtures, indicating blend compatibility. When the concentration of the drug was kept below 40% w/w, no melting endotherm could be observed, indicating the amorphous state of the drugs. Even at the highest drug load (50% w/w), the heat of fusion was well below 10% of that of a physical mixture of the same composition. Figure 5 shows the variation of T_g of temazepam, diazepam and prazepam with polyHEMA. T_g of the binary mixtures is frequently predicted using the Gordon-Taylor (GT) equation:

$$T_g = \frac{(W_1 T_{g_1}) + (K W_2 T_{g_2})}{W_1 + K W_2} \tag{4}$$

where W_1, and W_2 are the mass fractions of the benzodiazepine and polymer, respectively and T_{g_1} and T_{g_2} are the glass transition temperature of the benzodiazepine and polymer, respectively. T_g is the glass transition temperature of the solid dispersion, and K is defined as the ratio of the differences in expansion coefficient ($\Delta\alpha$) at T_g of the drug and polymer. However, when mass fractions are used instead of volume fractions, and when it is assumed that $\Delta\alpha T_g$= constant [19], K becomes:

$$K = \frac{\rho_1 T_{g_1}}{\rho_2 T_{g_2}} \tag{5}$$

ρ represents the density of the amorphous drug (ρ_1) and polymer (ρ_2). The density of the amorphous benzodiazepines were estimated from their crystalline density with a decrease of 5%. The solid lines in Fig. 5 represent the values predicted by the GT equation, whereas the symbols represent the experimental values. It is clear that negative deviations from the GT equation occur in the three cases, which can be explained by the fact that the GT equation is based upon the assumption of ideal volume additivity. Replotting the data according to the method of Schneider [19] offers the possibility to evaluate the significance of the deviations. Schneider [19] obtained a third power equation for the composition dependence of the glass transition temperature of binary blends, assuming that the binary contact interaction influences

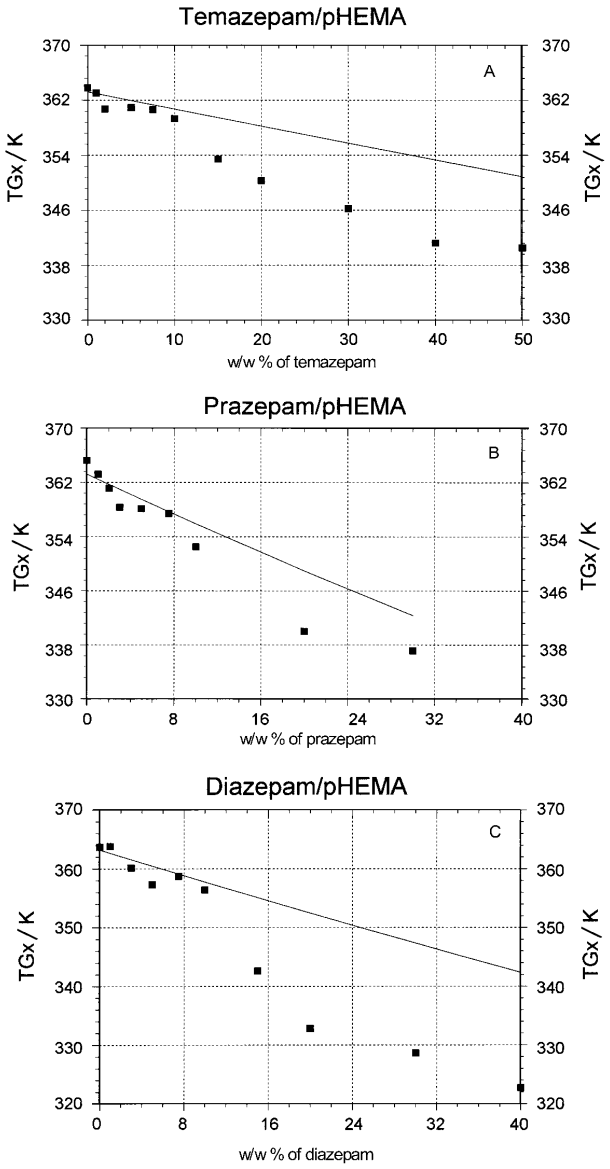

Fig. 5 Variation of the glass transition temperature of binary solid dispersions of polyHEMA with temazepam (5A), prazepam (5B) and diazepam (5C). The solid lines represent calculated values according to the Gordon-Taylor equation, while symbols represent experimental values

both conformation and free volume distribution in the blend. Assuming volume additivity, the third power equation can be simplified, and a plot of this simplified form: $(T_g–T_{g_1})/(T_{g_2}–T_{g_1})(KW_2/W_1+KW_2)$ *vs.* (KW_2/W_1+KW_2) results in a straight hori-

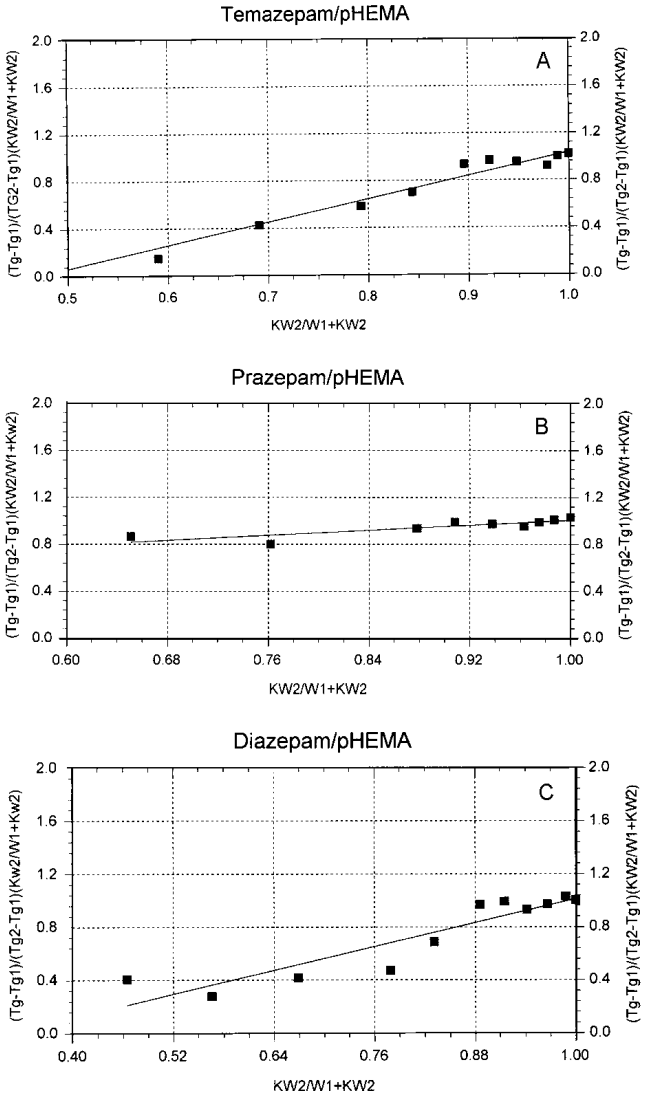

Fig. 6 Schneider plots [19] of binary solid dispersions of polyHEMA with temazepam (6A), prazepam (6B) and diazepam (6C). The solid lines represent least squares fitting while symbols represent experimental data

zontal line about unity if no specific interaction occurs between the blend components (the syrnbols are the same as in Eq. (4). Figure 6 confirms that the assumption of simple volume additivity only holds if drug concentrations are kept below 10%w/w. The slopes of least squares regression were significantly different from 0 (95% confidence interval): 1.9 for temazepam, 1.5 for diazepam, and 0.5 for prazepam. The deviation from ideal behaviour is caused by specific interactions,

most probably hydrogen bonding, between the blend components resulting in a change of free volume of the system. It is still unclear if interactions between a drug and a polymer in solid dispersions are favourable. However, it could be hypothesized that interactions lead to some kind of order in an amorphous system, which could be favourable with respect to the probability that drug molecules are transformed from the amorphous state to the crystalline state. In this respect, Schneider plots can add qualitatively valuable information. Positive and negative deviations as well as obedience of the ideal mixing rule are reported in literature. Binary solid dispersions of griseofulvin, indomethacine and glutethimide with PEG 6000, and citric acid with phenobarbitone showed negative deviation [20, 21], while systems with citric acid with pentobarbital, hexobarbital and heptobarbital showed a positive deviation [15]. It can be assumed that the strength of the interaction between the two components of the mixture dictates the deviation from ideality: if the bonding strength between the two components is weaker than between the individual molecules, the observed T_g will be lower than predicted. Although the GT equation is an easy and frequently used tool to predict T_g of compatible blends, the data presented in this paper illustrate that the use of the GT equation to predict T_g of solid dispersions and to set storage conditions for drugs incorporated as an amorphous entity in the dispersions, must be done with caution, since specific interactions between the blend components can result in a significant deviation from the predicted values.

Conclusions

The purpose of the present paper was to investigate the thermal properties of a series of benzodiazepines and to characterize their glass forming properties as well as to characterize solid dispersions with a model hydrophilic polymer: polyHEMA. It was shown that the studied benzodiazepines can be transformed from the crystalline to the amorphous state by cooling the fused molecules to below 273.15 K, irrespective of the cooling rate. Six out of twelve benzodiazepines showed decomposition at their melting points and the observed T_g of these drugs is probably different from that of the pure drugs. As a consequence formulation of these drugs as solid dispersions should preferably carried out using a solvent method instead of method based on heat treatment (fusion method). One possibility to reduce the retransformation from the amorphous to the crystalline state is to increase the T_g by the formation of a compatible blend with a compound with a higher T_g. We showed that prediction of T_g of the blend with polyHEMA using the Gordon-Taylor equation must be done with caution, since non-ideality in mixing behaviour significantly reduces the validity of this approach.

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