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Melting behavior of pure polyethylene glycol 6000 and polyethylene glycol 6000 in solid dispersions containing diazepam or temazepam: a DSC study

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Abstract

The purpose of the present study was to investigate the melting behavior of polyethylene glycol 6000 (PEG 6000) as such as well as in solid dispersions containing diazepam or temazepam, prepared by solvent and fusion methods, using differential scanning calorimetry (DSC). It was shown that the melting behavior of pure PEG 6000 is influenced by the crystallization procedure applied. Fusion at 80°C followed by cooling always yielded three different crystal modifications. The rate of cooling (under controlled conditions) was found to have a significant influence on the relative distribution of the three modifications: the lower the cooling rate, the higher the relative amount of the extended modification. Crystallization from organic solution yielded mainly the once folded form. The presence of diazepam and temazepam influenced the relative amount of the different PEG 6000 modifications. Both drugs decreased the formation of the more stable modification, while the formation of the twice folded form was induced. However, in the case of temazepam the contribution of the extended form at higher drug levels increased in dispersions obtained from organic solutions.

Keywords: Polyethylene glycol 6000; Diazepam; Differential scanning calorimetry (DSC)

1. Introduction

Many potential drug candidates are characterized by a low oral bioavailability. Often, drug dissolution/solubility rather than permeation through the epithelia of the gastro-intestinal tract are responsible for a low oral absorption. Among the techniques to increase aqueous solubility/dissolution rate, the formulation of solid dispersions is still one of the most popular ones [1,2]. Typical carriers for such systems include polyvinylpyrrolidone and polyethylene glycols (PEG) of various molecular weights in the range between 3000 and 20,000.

PEG 6000 crystallizes forming lamellae with chains either fully extended or folded once or twice, and chain-folding seems to be related to the crystallization procedure applied [3,4]. The chain-folded crystals are less stable with respect to extended chain crystals and tend to unfold. This may have an influence on the pharmaceutical performance and stability of solid dispersions using PEG as carrier material.

Several researchers [5–11] investigated the melting of PEG 6000 in solid dispersions of the polymer and a variety of drugs, prepared in many different ways, by differential scanning calorimetry (DSC). Relatively

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high heating rates (4–10°C/min) and/or high sample masses were applied, both resulting in DSC-curves with poor resolution. Some researchers [9,11] reported a shoulder or a poor resolved second endotherm next to the main melting endotherm of PEG 6000, suggesting the existence of two crystal forms of PEG 6000, assigning the low melting endotherm to the once folded modification and the higher melting to the extended modification.

Hantke and Zimmermann [12] proposed a method to evaluate the partial heats of fusion of the once folded and the extended modification of PEG 6000, based on the separation of the overlapping endotherms by means of deconvolution. The heating rate (2°C/min) and the sample mass applied (20 mg), however, resulted in DSC-curves with poor resolution.

Therefore, The objective of the present study was to develop and evaluate a 'high resolution' DSC-procedure in order to characterize qualitatively and quantitatively the melting of the different modifications of PEG 6000. Since PEG 6000 is often used as a carrier in solid dispersions, the influence of fusion and solvent preparation methods and the presence of guest molecules upon the polymorphic behavior of PEG 6000 was studied using this high resolution DSC-procedure. Two model drugs were selected; diazepam and temazepam. These benzodiazepine drugs were chosen because of their molecular similarity, though temazepam has an additional hydroxyl group.

2. Experimental

2.1. Materials

PEG 6000 was obtained from Across Organics (NJ, USA). Diazepam was obtained from Federa (Brussels, Belgium), while temazepam was obtained from Pharmacin (Zwijndrecht, Belgium). All other materials were of analytical grade.

2.2. Preparation of solid dispersions

2.2.1. Solvent evaporation method

Solid dispersions were prepared by dissolving physical mixtures of temazepam or diazepam and PEG 6000 in ethanol, methylene chloride or ethyl acetate. 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 at least 24 h.

2.2.2. Fusion method

Temazepam or diazepam was homogeneously dispersed in liquid PEG 6000 at 80°C, in a closed container, after which the dispersions were cooled either at room temperature or using a mixture of solid carbon dioxide in acetone (flash cooling). Subsequently, the solid dispersions were stored in vacuo over P_2O_5 for at least 24 h.

Finally, all dispersions were pulverized, sieved (<355 μm) and further dried in vacuo over P_2O_5 for at least 48 h. All dispersions were stored in a dessicator until use.

2.3. Differential scanning calorimetry

DSC measurements were carried out using a Perkin-Elmer DSC-7 (Perkin-Elmer, Norwalk, CT, USA) equipped with a liquid nitrogen subambient accessory (Perkin-Elmer, Norwalk, CT, USA). Samples (2–6 mg) were analyzed using hermetically sealed aluminium pans (TA instruments, Brussels, Belgium).

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, Norwalk, CT, USA).

The influence of the scanning speed on the thermal behavior of the pure polymer was investigated on samples which were held for 15 min at 80°C in a closed container, subsequently flash-cooled using a mixture of carbon dioxide in acetone, and further treated as described above. The influence of the scanning speed was then evaluated by varying it between 0.5 and 2°C/min.

The influence of the cooling rate on the distribution of different crystal modifications was investigated by holding the polymer in the DSC apparatus at 80°C during 15 min, followed by cooling it at 1, 5, 15 and 50°C/min. Subsequently, the samples were stored for at least 24 h to allow crystallization to take place, and scanned from 35 to 70°C at 1°C/min. A comparison was made between samples which were cooled to −75, −10 and 25°C.

All other samples of the pure polymer and solid dispersions were scanned from 35 to 70°C at 1°C/min.

3. Results and discussion

DSC of PEG 6000 which previously had been stored at 80°C for 15 min, followed by flash-cooling, showed a slightly different DSC-profile when the scanning rate was decreased from 2 to 0.5°C/min (Fig. 1). Three distinct peaks are noticed, the peak temperatures of which are not influenced by the scanning rate applied. The percentage of the total area (enthalpy of fusion) occupied by each peak changes with the scanning rate. The relative area of the first peak ($T_m = 57.86$°C at 1°C/min) increases from 8.32 to 13.61% when the scanning speed is increased from 0.5 to 2°C/min, while the area of the third peak ($T_m = 63.58$°C at 1°C/min) decreases from 3.83 to 1.96%. The relative area of the main peak ($T_m = 61.51$°C at 1°C/min) increases in the same way as peak I from 84.44 to 87.85%. Low molecular weight fractions of hydroxy-terminated PEG crystallize forming crystalline lamellae with the hydroxy-terminated chain ends rejected onto the surface of the lamellae [13]. It follows that the molecules are fully extended or folded a whole number of times. The obtained DSC-curves must, thus, be interpreted in terms of the presence of different crystal modifications. Given the fact that PEG with a molecular weight of 4000 is said to be the highest limit for which extended chain morphology predominates in mature crystals [14], and that crystallization of PEG 6000 at temperatures below 55°C indicated preference for folded chain crystallization, strongly suggest that peak III represents the extended modification, peak II the once folded, and peak I the twice folded modification. The melting temperature of the once and extended modification concurs with that reported by Buckley and Kovacs [4]. These authors also showed that chain unfolding (crystal thickening), either gradually or stepwise, did hardly, if at all, occur in once folded PEG 6000 crystals during heating, but the crystals remain essentially in their native form until complete melting at heating rates $\geq$0.5°C/min. The results of our experiments, on the other hand, show that the percentages of the peak area occupied by the extended and once folded modification increase with decreasing heating rate, while this is the opposite for the twice folded modifications. However, the increase or decrease observed is always very small, and samples were also encountered during this study which did not show peak III during heating under the same conditions. It is, therefore, suggested that the observed differences are not attributable to chain unfolding, but to a large extend to improved resolution at low heating rate, allowing a more accurate integration procedure. Moreover, scanning the samples at rates of 5 or 10°C/min decreased the resolution in a way that peaks I and III appear as a shoulder of the main peak, or even completely disappear.

In a next set of experiments, the influence of the cooling rate and the cooling depth on the formation of the extended and folded chain modifications was investigated. In order to control the cooling rate and depth, these experiments were at first instance completely performed in the DSC apparatus. The samples were kept at 80°C, a temperature which is considered to have practical relevance, for 15 min, after which the samples were cooled at various rates. The results are depicted in Fig. 2 and show that the relative amount of the extended chain increases with decreasing cooling rate, while the once folded modification shows the opposite behavior. This is consistent with the concept of a rate controlled crystallization process. A low cooling rate indeed allows the formation of the thermodynamically more stable modifications. Similar observations were obtained by Beech et al [15] using dilatometry and low-angle X-ray scattering. The relative contribution of the twice folded form increased consistently if the cooling rate increased, but at a rate of 50°C/min, again a drop in the relative contribution was noticed, which at the moment remains unclear. The influence of the cooling depth (25, −10, −75°C) was negligible; the presence as well as the relative distribution of the different modifications remained unchanged.

As the above-mentioned experiments can be considered to be carried out ‘under controlled conditions’, this situation clearly deviates from practice. Indeed preparation of solid dispersions occurs on a larger scale, in which due to a.o. more pronounced thermal lag and gradients, cooling is unlikely to proceed in a controlled way. In order to have an idea on the occurrence and on the reproducibility of the distribution of the crystal modifications as a consequence of a

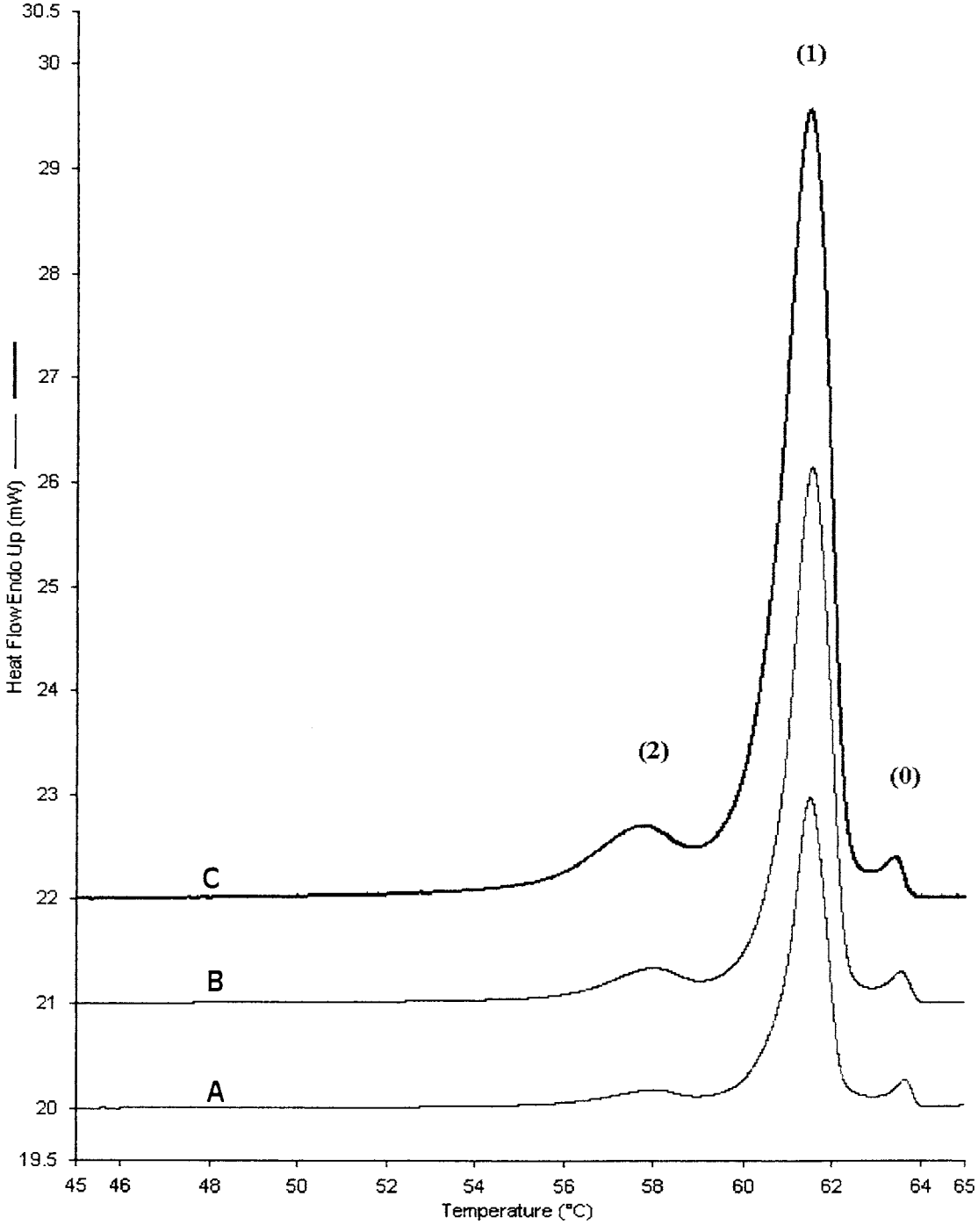

Fig. 1. DSC-curve of PEG 6000 which was stored at 80°C during 15 min and flash-cooled. Heating rate is 0.5°C/min (lower curve); 1°C/min (mid curve); 2°C/min (upper curve): (2) represents the twice folded modification, (1) the once folded modification, and (0) represents the extended modification.

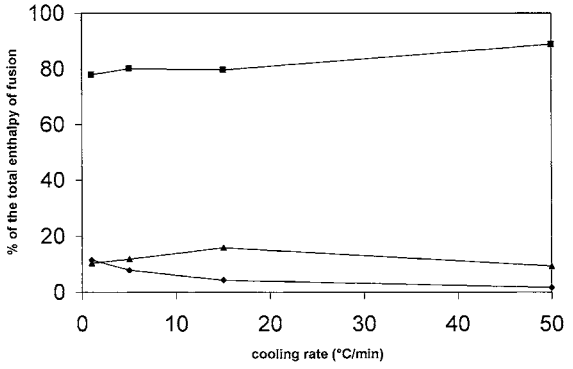

Fig. 2. Influence of the cooling rate on the relative distribution of the different PEG modifications: (■) once folded modification; (▲) twice folded modification; (◆) extended modification.

process which is closer to real pharmaceutical practice, PEG 6000 was either crystallized by flash-cooling or cooling at room temperature from samples which were prior held at 80°C for 15 min. PEG 6000 was also crystallized from a solution in ethanol, methylene chloride or ethyl acetate by solvent evaporation at 35–40°C under reduced pressure. Flash-cooling of melted PEG 6000 yielded the three modifications with a reproducible distribution (Fig. 3), which was also comparable to the 50°C/min cooling rate as discussed above. Surprisingly it was found that samples which were crystallized at room temperature did show that less than 1% of the total melting enthalpy was occupied by the extended modification; also the twice folded form was only marginally present and appeared as a shoulder on the leading edge of the peak of the once folded form in the DSC-curve (Fig. 3). Since the obtained results were highly reproducible, it must be clear that this phenomenon is not an artefact, and show that data obtained under controlled conditions do not always reflect real practice.

Crystallization from the solution during rapid solvent evaporation showed that the once folded form was always the predominant one. The extended form could never be detected, which further confirms that chain unfolding during heating does not occur. The twice folded modification was clearly present in material obtained from ethanolic solution (contribution approximately 8% of the total melting enthalpy), while material obtained from methylene chloride and ethyl acetate yielded a marginal but still detectable amount of twice folded chains.

As shown in Tables 1–3, the presence of diazepam clearly influences the crystallization behavior of PEG 6000, although the total enthalpy of fusion was not largely influenced. The data from Table 1 represent the relative percentages of the total melting enthalpy and the temperatures of fusion of the three crystal modifications immediately after preparation of the dispersions. Dispersions prepared by the fusion/flash-cooling procedure, show a typical melting point depression (Table 1), due to the presence of the guest molecule, especially for the once and twice folded modifications, while the influence on the extended form is less pronounced. Compared to the pure polymer which was treated in the same way as the dispersions, it was observed that the relative amount of the extended chain form is significantly reduced in the presence of 1% w/w of diazepam from approximately 3.25–1.87%. As the amount of drug increases, the extended modification becomes less important, since from 10% w/w of drug on it appears as a shoulder on the once folded form, and at a 40% w/w drug concentration, the extended form is no longer present. The relative amount of the once folded modification also decreased in the presence of diazepam as compared to the situation of the pure polymer, but the twice folded form significantly increased in the solid dispersions with increasing drug concentration. At 50% w/w of diazepam, its relative percentage amounted up to more than 23%. These results demonstrate in an unambiguous manner that diazepam promotes the formation of the twice folded modification, and this mainly on the expense of the extended form. Dispersions prepared by the fusion method, but cooled at room temperature (Table 2), mainly formed the once folded modification, but the same trend as in the flash-cooled systems was observed: the higher the amount of diazepam, the more important becomes the twice folded modification, and the extended form completely disappears, this from 5% w/w of drug on. Therefore, at higher drug concentrations, formation of the twice folded modification occurs on the expense of the once folded form.

The solvent evaporation method is a valuable alternative for the preparation of solid dispersions of thermolabile drugs. In these experiments methylene chloride, ethanol and ethyl acetate were investigated. Due to the similarity of the results obtained, only those for methylene chloride will be discussed (Table 3). Low drug concentrations (<30% w/w) mainly yield

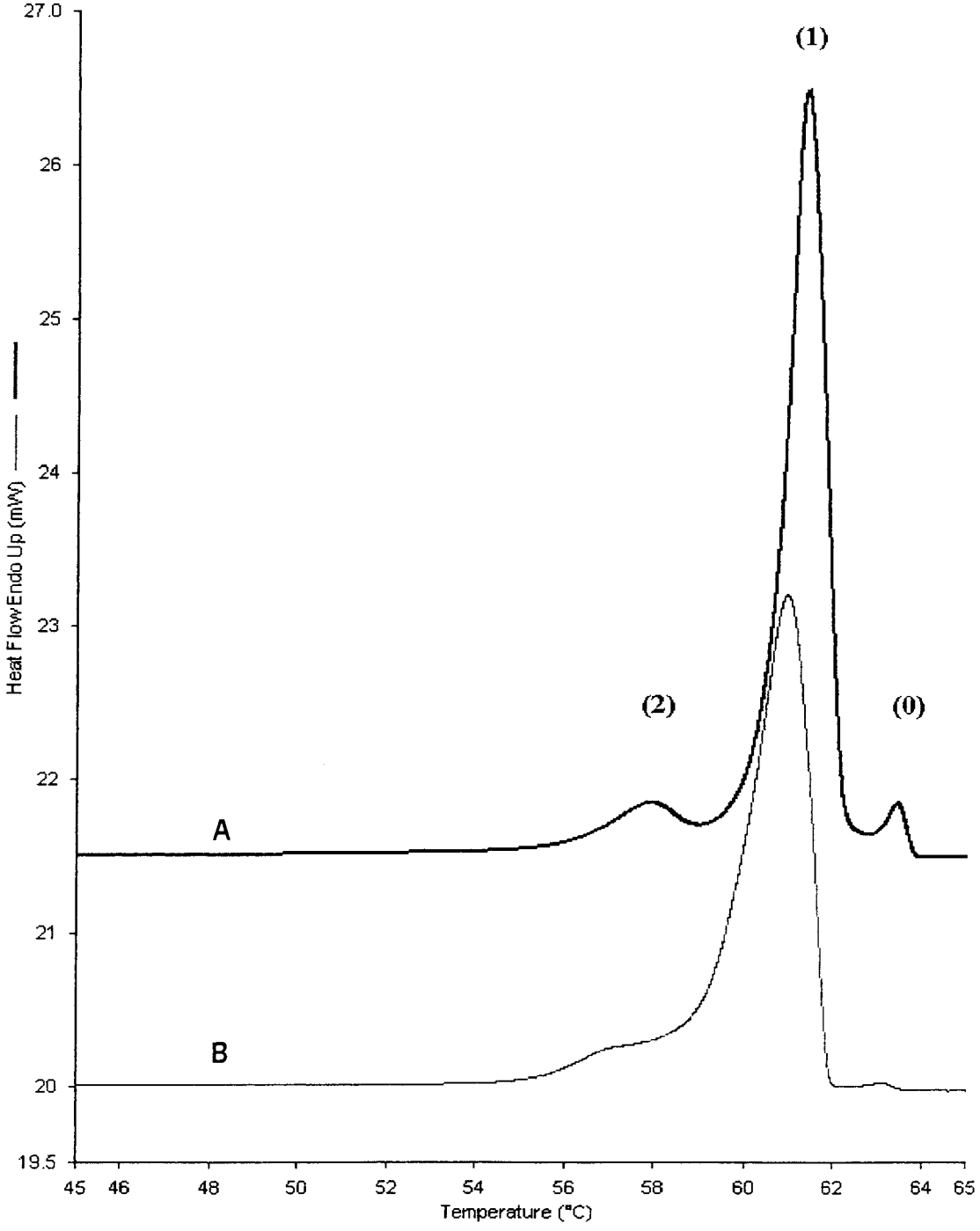

Fig. 3. Influence of cooling procedure. Upper curve — flash-cooling; lower curve — cooling at room temperature: (2) represents the twice folded modification, (1) the once folded modification, and (0) represents the extended modification.

Table 1
Peak temperature, relative distribution of PEG 6000 modifications and weight corrected total heat of fusion of PEG 6000 in solid dispersions with diazepam, prepared by fusion/flash-cooling

Diazepam (% w/w)	$T(1)$ (°C)	$T(2)$ (°C)	$T(0)$ (°C)	%(1)	%(2)	%(0)	ΔH_f (J/g)
0	61.43	57.92	63.52	85.65	10.84	3.30	178.85
	61.57	58.32	63.56	85.37	11.44	3.19	179.14
1	61.48	57.73	63.35	82.58	15.58	1.84	189.15
	61.55	57.59	63.43	83.90	14.21	1.89	183.65
2	61.17	56.77	63.20	83.54	14.43	2.03	182.60
	61.42	57.60	63.34	81.76	16.14	2.10	187.07
3	61.21	57.51	63.20	82.77	15.36	1.87	188.58
	61.20	57.29	63.20	83.49	14.64	1.87	187.16
5	60.62	56.98	62.83	84.60	14.45	0.95	181.21
	60.73	57.29	62.85	84.60	14.46	0.95	186.41
10	59.94	56.80	Shoulder	83.66	16.04	–	180.43
	59.26	55.17	Shoulder	84.98	14.70	–	180.43
20	58.76	54.30	Shoulder	85.39	14.49	–	176.06
	59.93	56.98	Shoulder	83.73	16.16	–	179.67
40	59.93	57.07	–	76.44	23.56	–	188.14
	59.73	56.65	–	78.53	21.47	–	183.74
50	59.93	57.07	–	76.87	23.13	–	184.77
	59.87	57.00	–	76.06	23.94	–	189.44
80	59.80	56.68	–	79.11	20.89	–	184.24
	58.63	53.81	–	85.33	14.64	–	178.18

Table 2
Peak temperature, relative distribution of PEG 6000 modifications and weight corrected total heat of fusion of PEG 6000 in solid dispersions with diazepam, prepared by fusion and cooling at room temperature

Diazepam (% w/w)	$T(1)$ (°C)	$T(2)$ (°C)	$T(0)$ (°C)	%(1)	%(2)	%(0)	ΔH_f (J/g)
0	60.95	Shoulder	63.12	99.33	–	0.67	178.25
	60.93	Shoulder	63.00	99.34	–	0.66	188.98
1	61.38	–	63.38	99.49	–	0.51	189.25
	61.42	–	63.38	99.50	–	0.50	188.23
3	61.04	–	63.02	99.74	–	0.26	188.68
	60.93	–	63.02	99.75	–	0.25	190.48
5	59.87	–	Shoulder	100	–	–	189.37
	59.76	–	Shoulder	100	–	–	190.33
10	59.47	–	Shoulder	100	–	–	186.70
	59.33	–	Shoulder	100	–	–	187.81
20	60.17	Shoulder	–	100	–	–	194.41
	60.33	Shoulder	–	100	–	–	191.94
30	59.73	Shoulder	–	100	–	–	189.33
	59.64	Shoulder	–	100	–	–	191.98
40	60.16	Shoulder	–	100	–	–	191.17
	60.30	Shoulder	–	100	–	–	190.33

Table 2 (*Continued*)

Diazepam (% w/w)	$T(1)$ (°C)	$T(2)$ (°C)	$T(0)$ (°C)	%(1)	%(2)	%(0)	ΔH_f (J/g)
50	59.68	Shoulder	–	100	–	–	189.90
	59.60	Shoulder	–	100	–	–	198.89
60	59.77	57.63	–	76.90	23.10	–	191.61
	59.63	57.85	–	77.45	22.55	–	191.48

Table 3
Peak temperature, relative distribution of PEG 6000 modifications and weight corrected total heat of fusion of PEG 6000 in solid dispersions with diazepam, prepared by solvent evaporation using methylene chloride

Diazepam (% w/w)	$T(1)$ (°C)	$T(2)$ (°C)	$T(0)$ (°C)	%(1)	%(2)	%(0)	ΔH_f (J/g)
0	61.27	Shoulder	–	100	–	–	178.07
	61.68	Shoulder	–	100	–	–	181.41
1	60.45	Shoulder	–	100	–	–	182.85
	61.67	Shoulder	–	100	–	–	185.16
2	61.33	Shoulder	–	100	–	–	187.58
	61.32	Shoulder	–	100	–	–	185.92
3	61.28	Shoulder	–	100	–	–	187.89
	61.20	Shoulder	–	100	–	–	190.99
5	60.34	Shoulder	–	100	–	–	187.04
	60.68	Shoulder	–	100	–	–	186.46
10	59.51	Shoulder	–	100	–	–	190.64
	58.89	Shoulder	–	100	–	–	187.95
20	58.87	Shoulder	–	100	–	–	191.13
	59.88	Shoulder	–	100	–	–	190.73
30	59.16	Shoulder	–	100	–	–	185.21
	58.85	Shoulder	–	100	–	–	186.51
40	59.91	57.52	–	75.69	24.31	–	190.86
	60.02	57.70	–	75.07	24.93	–	190.67
50	59.00	55.33	–	75.60	24.40	–	180.51
	58.68	54.59	–	75.61	24.39	–	187.45
60	59.18	55.36	–	81.74	18.26	–	183.74
	59.48	56.28	–	82.81	17.19	–	183.49
70	58.78	55.33	–	82.60	17.40	–	182.47
	59.12	55.84	–	81.92	18.08	–	180.29
80	59.01	55.72	–	78.59	21.41	–	177.12
	59.11	55.93	–	78.50	21.50	–	180.79
90	59.14	55.84	–	79.35	20.65	–	173.61
	59.21	56.07	–	78.48	21.52	–	175.50

the once folded modification; at those concentrations, the twice folded form appears as an increasing shoulder on the DSC-curve. However, from 40% w/w on, the twice folded form is integratable and contributes to approximately 20% of the total melting enthalpy of PEG 6000. As in the dispersions prepared by the fusion methods, the extended modification is not present. Based on the values of the melting point, diazepam affects the crystallization of both the once and twice folded modifications. It was also interesting

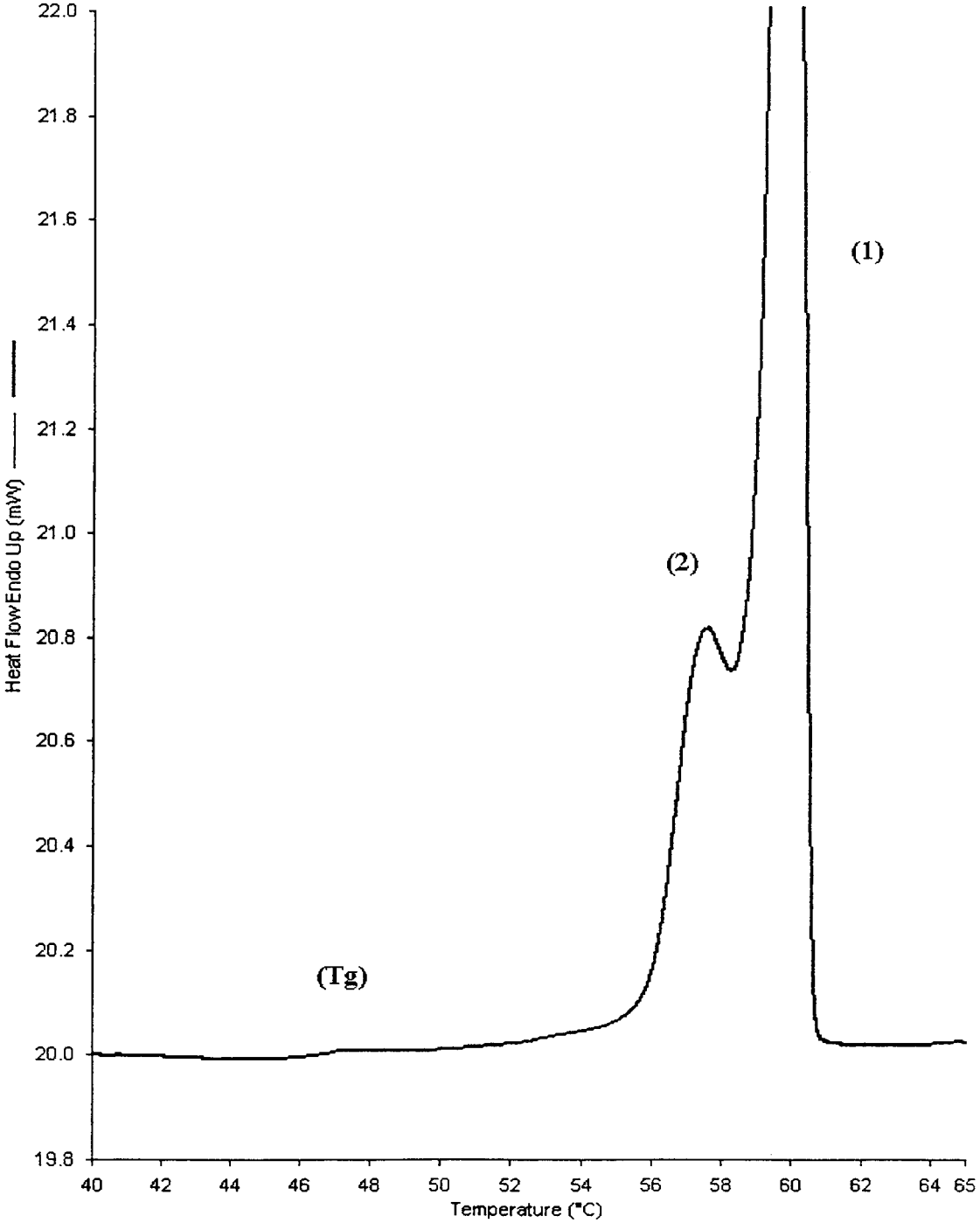

Fig. 4. Representative DSC-curve of a solid dispersion containing 40% w/w of diazepam, prepared from methylene chloride solution: (2) represents the twice folded modification, (1) the once folded modification.

Table 4
Peak temperature, relative distribution of PEG 6000 modifications and weight corrected total heat of fusion of PEG 6000 in solid dispersions with temazepam, prepared by solvent evaporation using methylene chloride

Temazepam (% w/w)	$T(1)$ (°C)	$T(2)$ (°C)	$T(0)$ (°C)	%(1)	%(2)	%(0)	ΔH_f (J/g)
0	61.27	Shoulder	–	100	–	–	178.07
	61.68	Shoulder	–	100	–	–	181.41
1	61.60	Shoulder	–	100	–	–	182.62
	61.63	Shoulder	–	100	–	–	185.44
2	61.27	Shoulder	–	100	–	–	187.37
	61.46	Shoulder	–	100	–	–	185.39
3	61.08	Shoulder	–	100	–	–	189.57
	61.00	Shoulder	–	100	–	–	190.39
5	60.49	Shoulder	–	100	–	–	186.40
	60.60	Shoulder	–	100	–	–	187.25
10	60.43	Shoulder	–	100	–	–	186.55
	60.52	Shoulder	–	100	–	–	186.66
20	60.62	Shoulder	–	100	–	–	188.50
	60.60	Shoulder	–	100	–	–	188.81
30	60.61	Shoulder	–	100	–	–	191.11
	60.49	Shoulder	–	100	–	–	189.02
40	60.55	57.93	–	86.32	13.68	–	186.16
	60.53	57.98	–	85.13	14.87	–	186.88
50	60.38	57.58	62.22	74.95	23.92	1.13	187.04
	60.48	57.67	62.33	74.73	23.95	1.32	189.34
60	60.46	57.91	62.35	69.94	27.51	2.55	185.68
	60.52	57.99	62.47	71.95	25.64	2.41	182.54
70	60.22	57.74	62.70	66.95	19.40	13.65	181.79
	60.24	57.71	62.71	64.12	20.94	14.94	185.28

to note that dispersions prepared by the solvent evaporation method showed a jump in heat capacity at approximately 46°C (Fig. 4). This value concurs with the position of the glass transition of pure diazepam as reported previously [16] and indicates that the drug is partially amorphous in these dispersions.

Due to increased hydrogen bonding possibilities, temazepam was compared to diazepam to study the influence of a guest molecule on the crystallization behavior of PEG 6000. Although the peak temperature of each modification decreased with increasing drug concentration in dispersions prepared by fusion/flash-cooling, thereby, suggesting that temazepam affects the crystallization of all modifications. It must, however, be clear that increasing amounts of temazepam impeded the formation of the extended form, while the relative amount of the twice folded modification increased (Tables 4–6). Opposite to the findings of Dordunoo et al. [11], we did not observe a significant decrease in the total enthalpy of fusion of PEG 6000 in the presence of temazepam, probably due to differences in preparation conditions of the solid dispersions. In the work of Dordunoo et al. [11] solid dispersions were prepared in a DSC-apparatus, heated to 100 or 150°C for 5 min and subsequently cooled at 200°C/min, resulting in a higher amount of amorphous PEG 6000 that partly crystallized upon aging at room temperature as indicated by an increase in enthalpy of fusion. The higher batch size (5 g in stead of 5 mg), resulting in uncontrolled and slower cooling, due to gradients and thermal lags probably explains the higher enthalpies of fusion compared with the findings of Dordunoo et al. [11]. Solidification from methylene chloride solutions yielded the same picture at low drug

Table 5
Peak temperature, relative distribution of PEG 6000 modifications and weight corrected total heat of fusion of PEG 6000 in solid dispersions with temazepam, prepared by fusion/flash-cooling

Temazepam (% w/w)	$T(1)$ (°C)	$T(2)$ (°C)	$T(0)$ (°C)	%(1)	%(2)	%(0)	ΔH_f (J/g)
0	61.43	57.92	63.52	85.65	10.84	3.30	178.85
	61.57	58.32	63.56	85.37	11.44	3.19	179.14
1	61.48	57.98	63.40	84.32	13.25	2.43	182.77
	61.63	58.06	63.48	84.04	13.32	2.64	182.35
2	61.25	57.83	63.29	83.80	13.94	2.26	182.68
	61.28	57.83	63.31	83.52	14.18	2.30	183.03
3	61.00	57.66	63.08	84.20	14.10	1.70	180.88
	60.93	57.47	63.04	84.72	13.57	1.71	180.42
5	60.53	57.52	62.70	85.79	13.12	1.09	180.65
	60.53	57.64	62.70	84.98	14.06	0.96	180.77
10	60.42	57.53	62.22	85.51	13.80	0.69	177.41
	60.44	57.50	62.20	85.69	14.03	0.28	178.30
20	60.23	57.07	–	81.73	18.27	–	181.08
	60.37	57.43	–	80.02	19.98	–	182.89
30	60.49	57.55	–	79.63	20.37	–	180.63
	60.37	57.43	–	79.87	20.13	–	181.15
40	60.39	57.52	–	79.29	20.71	–	180.62
	60.41	57.49	–	79.21	20.79	–	179.57
50	60.33	57.29	–	81.25	18.75	–	179.30
	60.30	57.28	–	80.69	19.31	–	180.03
60	60.38	57.13	–	82.72	17.28	–	177.65
	60.18	56.79	–	83.72	16.28	–	177.44

Table 6
Peak temperature, relative distribution of PEG 6000 modifications and weight corrected total heat of fusion of PEG 6000 in solid dispersions with temazepam, prepared by fusion and cooling at room temperature

Temazepam (% w/w)	$T(1)$ (°C)	$T(2)$ (°C)	$T(0)$ (°C)	%(1)	%(2)	%(0)	ΔH_f (J/g)
0	60.95	Shoulder	63.12	99.33	–	0.67	178.25
	60.93	Shoulder	63.00	99.34	–	0.66	188.98
1	61.72	–	63.49	99.47	–	0.53	185.43
	61.62	–	63.72	99.42	–	0.58	184.23
3	61.42	–	62.43	99.69	–	0.31	185.90
	61.42	–	62.30	99.68	–	0.32	185.99
5	61.12	–	62.98	99.81	–	0.19	190.87
	61.13	–	62.45	99.79	–	0.21	189.26
10	60.84	Shoulder	–	100	–	–	187.80
	61.06	Shoulder	–	100	–	–	189.21
20	59.77	Shoulder	–	100	–	–	184.33
	60.79	Shoulder	–	100	–	–	185.42
30	60.34	Shoulder	–	100	–	–	186.82
	60.67	Shoulder	–	100	–	–	185.28

Table 6 (*Continued*)

Temazepam (% w/w)	$T(1)$ (°C)	$T(2)$ (°C)	$T(0)$ (°C)	%(1)	%(2)	%(0)	ΔH_f (J/g)
40	60.62	Shoulder	–	100	–	–	185.84
	60.79	Shoulder	–	100	–	–	186.21
50	59.49	Shoulder	–	100	–	–	189.89
	59.95	Shoulder	–	100	–	–	189.32
60	60.72	Shoulder	–	100	–	–	192.86

concentrations (Table 4), i.e. up to 30% w/w the once folded form predominates, the extended form is only marginally present up to a few percent of drug (<5% w/w), while the contribution of the twice folded form increases with increasing drug concentration. At higher drug concentrations (>40% w/w), the twice folded form is clearly present and completely opposite to the dispersions with diazepam, the relative percentage of the extended form starts to increase. At 70% w/w of drug it contributes to approximately 14% of the total melting enthalpy of the polymer.

If the drug is considered to be an impurity which hinders PEG 6000 crystallization, it can be hypothesized that less stable modifications will be formed first. In this respect, our results support this since the twice folded modification always increased with increasing drug concentration. The observation that temazepam dispersions obtained from organic solution shows the extended form, while this is not the case with diazepam dispersions, can be, at least partially, explained by increased hydrogen bonding possibilities between the ether and hydroxyl function of PEG 6000 and the hydroxyl function of temazepam, thereby, promoting the formation of the thermodynamically stable form. It can be hypothesized that the fact that this was only observed in dispersions from organic solution and not in those prepared by the fusion method (Tables 5 and 6), is the consequence of increased mobility in solution, giving the molecules more orientational possibilities.

4. Conclusion

The results of the present study showed that the melting behavior of PEG 6000 is influenced by the crystallization procedure applied, i.e. fusion at 80°C followed by cooling or crystallization from organic solution. Whereas the latter predominantly produced the once folded modification, fusion methods always yielded the three modifications. The rate of cooling (under controlled conditions) was found to have a significant influence on the relative distribution of the three modifications: the lower the cooling rate, the higher the relative amount of the extended modification, the thermodynamically stable form.

The presence of diazepam and temazepam influenced the relative amount of the different PEG 6000 modifications. Both drugs decreased the formation of the more stable modification, while the twice folded form was formed. However, in the case of temazepam the contribution of the extended form at higher drug levels increased in dispersions obtained from organic solutions.

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