Journal of Thermal Analysis and Calorimetry, Vol. 73 (2003) 563–576

PHARMACEUTICAL PERFORMANCE OF SOLID DISPERSIONS CONTAINING POLY(ETHYLENE) GLYCOL 6000 AND DIAZEPAM OR TEMAZEPAM
Influence of grinding

S. Verheyen [1], *N. Blaton* [2], *R. Kinget* [1] *and G. Van den Mooter* [1*]

[1]Laboratorium voor Farmacotechnologie en Biofarmacie, K. U. Leuven Campus Gasthuisberg O+N, Herestraat 49, 3000 Leuven, Belgium
[2]Laboratorium voor Analytische Chemie en Medicinale Fysicochemie, K. U. Leuven, Van Evenstraat 4, 3000 Leuven, Belgium

Abstract

The effect of grinding on the physical properties and pharmaceutical performance of solid dispersions made of poly(ethylene) glycol 6000 (PEG6000) and temazepam or diazepam was studied using differential scanning calorimetry (DSC), X-ray powder diffraction and dissolution experiments. DSC-analysis of flash-cooled dispersions revealed that amorphous PEG present immediately after grinding crystallised upon aging mainly into the twice folded modification and to a small extent into the extended form. DSC-analysis of dispersions kept in the slab form for 1 month and subsequently ground, revealed that in the abscence of the grinding impulse crystallisation of PEG6000 takes place in the same way as in dispersions ground immediately after preparation and then aged for 1 month. Grinding solid dispersions immediately after preparation resulted in superior dissolution properties compared with solid dispersions kept in the monolith-slab form and subsequently ground. This difference in dissolution properties was found to be attributed to the drug and not to the polymer, more precisely, it was suggested that the drug particle size in ground dispersions was smaller than in dispersions kept in the slab form and subsequently ground. These findings suggest that grinding of solid dispersions immediately after preparation is the preparation method of choice instead of liquid filling of hard gelatin capsules resulting in monoliths.

Keywords: benzodiazepines, dissolution, DSC, grinding, poly(ethylene) glycol, solid dispersion, stability, X-ray powder diffraction

Introduction

Many potential drug candidates are characterised 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 studied to increase aqueous solubility/dissolution rate, the formulation of solid dispersions is one of the most popular ones [1, 2]. Mechanisms responsible for the improved aqueous solubility/dissolution properties of solid dispersions include reduc-

* Author for correspondence: E-mail: guy.vandenmooter@pharm.kuleuven.ac.be

1388–6150/2003/ $ 20.00
Akadémiai Kiadó, Budapest

tion of the particle size of the incorporated drug, (partially) 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 [3, 4].

Despite the potential of solid dispersion formulations containing poly(ethylene) glycols to improve the oral bioavailability of drugs [5–8], only few products have been commercialised, probably because of production issues and/or the physical instability of solid dispersions resulting in changing dissolution profiles during aging [9–13].

Previously we reported on solid dispersions containing poly(ethylene) glycol 6000 (PEG6000) and diazepam (DIA) or temazepam (TEM), prepared by the solvent evaporation method and by the fusion method with fast cooling or slow cooling. These solid dispersions were physically characterised in order to unravel the mechanism of increased dissolution of DIA and TEM in the presence of PEG6000 [14].

In a second report, the influence of aging (at 6 or 25°C for 12 months) upon the dissolution of these solid dispersions was investigated and the nature and mechanism of any aging process was characterised [15]. An important conclusion was that both PEG6000 and DIA or TEM, brought into the liquid state during solid dispersion preparation, (partially) recrystallised in the time interval between preparation and the first analysis. These dispersions were all ground after preparation. Analysis of aged solid dispersions revealed that the crystallinity of the drug and of PEG6000 only slightly increased during aging.

The purpose of the present study was to gain insight into the relation between grinding of solid dispersions and recrystallisation of both drug and PEG6000. Therefore, the paper aims to contribute to the rational development of preparation methods of solid dispersions.

Materials and methods

Materials

PEG6000 was purchased from Across Organics (New Jersey, USA). Pharmaceutical grade DIA and TEM were obtained from Federa (Brussels, Belgium) and Pharmacin (Zwijndrecht, the Netherlands), respectively. PEG6000 flakes and DIA crystals were ground with pestle and mortar. Ground PEG6000, ground DIA and TEM (as received) were passed through a 355 μm sieve. Solvents were of HPLC grade.

Methods

Gel permeation chromatography

10 mg PEG6000 was dissolved in 10 mL mobile phase (0.01 M Na_2HPO_4, adjusted to pH 7.0 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^{-1}. PEG standards (molecular mass 620, 1080, 1900, 4120, 6450, 11800, 22800) were from Polymer Labs and the detec-

tion was performed with a refractive index detector. M_w and dp of PEG6000 were found to be 6146 and 1.09, respectively.

Preparation of solid dispersions and physical mixtures

Physical mixtures

Physical mixtures, containing 10 mass/mass% of drug, were prepared by mixing 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 sealed glass bottles until use.

Solid dispersions prepared by the fusion method

Solid dispersions containing 10 mass/mass% DIA or TEM were prepared by heating 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 20 min, the melts were poored in plastic moulds and cooled at room temperature forming tablets with a diameter of 9 mm and an approximate mass of 200 mg. These tablets were then stored in vacuo over P_2O_5 for 72 h, and subsequently analysed immediately, after 7 days and after 1 month.

Melts were also cooled either at room temperature or by placing the closed teflon container for 20 min in a mixture of solid carbon dioxide and acetone (flash cooling). These solid dispersions were then stored in vacuo over P_2O_5 for 72 h. Subsequently, one part of these dispersions was ground, sieved (<355 μm) and analysed immediately, after 2 days, after 7 days and after 1 month. The other part of the solid dispersions was kept in the slab form at 25°C for 1 month after which they were ground, sieved (<355 μm) and analysed immediately, after 2 days and after 7 days. In the same way, slabs and ground slabs containing only PEG6000 were prepared. Tablets, slabs and ground slabs were stored at 25°C in sealed bottles 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 (2–4 mg) were weighed in aluminium pans (TA instruments, Brussels, Belgium), sealed and subsequently scanned at 1°C min^{-1} under nitrogen gas purge (20 mL min^{-1}) [18]. 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).

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, Eindhoven, The Netherlands) modified for

step-scan operations. The CuK_α radiation (λ=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 1 s/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. X-ray diffraction is only able to estimate the degree of crystallinity with an overal sensitivity of 5–10% [19]. In addition, grinding might reduce the crystallinity of the drugs incorporated in the dispersions.

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 demineralised water at 37°C). Tablets were, as such, introduced in the dissolution medium. At designated time intervals, 1 mL samples were withdrawn, filtered (0.20 μm, nylon), assayed and replaced by the same amount of fresh dissolution medium. The dissolution experiments were performed in triplicate. Filtration equipment was checked for drug adsorption.

Assay of benzodiazepines

Appropriate diluted samples were assayed spectrophotometrically for DIA or TEM at 235 nm. PEG6000 does not interfere with the assay of the benzodiazepines at this wavelength.

Results and discussion

Solid dispersions containing DIA or TEM and PEG6000 were prepared by a fusion method with slow or fast cooling. They were ground, sieved and characterised immediately, after 2 days, 7 days and after 1 month using differential scanning calorimetry, X-ray powder diffraction and dissolution experiments. Solid dispersions were also kept for 1 month in the slab form, subsequently ground, sieved and characterised immediately, after 2 days and after 7 days, to find out if recrystallisation of polymer and drug appears to the same extent in that time interval of 1 month in absence of the grinding impulse.

Since differential scanning calorimetry and X-ray powder diffraction imply that solid dispersion slabs were powdered prior to analysis, tablets were moulded and without grinding analysed immediately, after 7 days and after 1 month by dissolution experiments. Changing dissolution profiles indicate a change in the physical state of drug and/or polymer. Increase in degree of crystallinity of drug and/or PEG6000, conversion

of a drug polymorph into a more stable polymorphic form, increase in drug particle size due to Ostwald ripening and/or due to precipitation of amorphous drug onto present crystalline drug particles all can result in poorer dissolution profiles [20].

Thermal analysis

PEG6000 crystallises forming lamellae with chains either fully extended (0) or folded once (1) or twice (2) (Fig. 1) [16–18]. The twice folded modification (2) has a lower melting temperature with respect to the once folded (1) and the melting temperature of the once folded modification is lower with respect to the extended form (0). The folding behavior of PEG6000, can be qualitatively and quantitatively evaluated by a high resolution DSC-method as reported recently [18]. Theoretically, DSC-analysis can also be used to evaluate the polymorphic behaviour and the degree of crystallinity of DIA or TEM in the respective solid dispersions. However, this was not possible, since both DIA and TEM dissolve in the molten PEG6000 during DSC-analyis of the solid dispersion samples. Therefore, the degree of crystallinity and the polymorphic behaviour of the drugs in the solid dispersions were evaluated by Bragg–Brentano powder diffractometry.

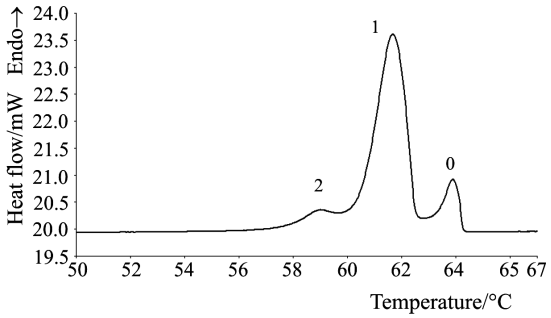

Fig. 1 DSC curve of PEG6000 showing melting endotherms of 2 – twice folded; 1 – once folded; 0 – extended modification

Table 1 shows the peak temperatures, relative distributions of PEG6000 modifications and total heats of fusion of PEG6000 prepared by fusion with slow or fast cooling, determined at different time points after grinding. The total heats of fusion of PEG6000, which are measures of the degree of crystallinity of the polymer, are quasi identical at the different time points, irrespective of the cooling procedure applied. This suggests that PEG6000 crystallises in the time interval between preparation and grinding and/or in the interval between the first grinding impulse and the immediate analysis, after which no further important crystallisation seems to occur. Table 1 also clearly illustrates the influence of the cooling procedure on the PEG6000 modifications formed. Cooling at room temperature results predominantly in the formation of the once folded modification, while the twice folded modification is present as a non-integratable shoulder and only a small amount of the extended modification is formed. Flash-cooling results in a larger amount of the extended modification, less

Table 1 Peak temperatures, relative distributions of PEG6000 modifications and total heats of fusion of PEG6000 (ΔH_f) prepared by fusion with slow (rT) or fast cooling (CO_2), determined at different time points after grinding (gr)

	T/(1)/°C	T(2)/°C	T(0)/°C	%(1)	%(2)	%(0)	ΔH_f/J g^{-1}
			PEG rT				
gr 0 d	62.22		63.90	99.09		0.91	180.53
gr 2 d	61.85		63.64	99.06		0.95	181.72
gr 7 d	61.57		63.46	98.86		1.14	182.22
gr 1 m	61.75		63.59	98.92		1.08	185.09
1 m gr 0 d	62.24		63.85	99.13		0.87	185.54
1 m gr 2 d	62.05		63.60	99.15		0.95	186.32
1 m gr 7 d	62.42		63.54	99.17		0.93	185.87
			PEG CO_2				
gr 0 d	62.28	59.05	64.02	84.28	12.21	3.51	180.78
gr 2 d	61.84	58.27	63.71	84.04	12.42	3.54	179.41
gr 7 d	61.77	58.08	63.70	82.92	13.42	3.67	181.24
gr 1 m	61.78	58.04	63.69	80.21	16.14	3.65	185.84
1 m gr 0 d	61.99	58.45	63.79	81.06	15.32	3.62	182.64
1 m gr 2 d	62.05	58.36	63.50	80.53	16.02	3.45	183.51
1 m gr 7 d	61.89	58.55	63.63	80.87	15.53	3.60	182.83

T(1) is the melting temperature of the once folded modification, T(2) that of the twice folded and T(0) that of the extended modification.
%(1) is the relative contribution of the once folded modification to the total heat of fusion, %(2) that of the twice folded and %(0) that of the extended modification.

formation of the once folded modification (although, this modification still remains predominant) and an increase in the amount of the twice folded modification formed compared with PEG6000 cooled at room temperature. The observation that flash-cooling of PEG6000 promotes the formation of the less stable twice folded modification can be attributed to the fast increase in viscosity and hence fast decrease in mobility during flash cooling, giving the polymer less orientational possibilities, resulting in less ordered crystals reflected in more pronounced formation of the less stable twice folded modification. However, flash-cooling also promotes the formation of the extended modification. The relative distributions of PEG6000 modifications at the different time points are comparable, suggesting the absence of important conversions of one modification into the other, also referred to as unfolding.

Tables 2 and 3 show the peak temperatures, relative distributions of PEG6000 modifications and report mass corrected total heats of fusion of PEG6000 in solid dispersions with DIA or TEM, prepared by fusion with slow or fast cooling, determined at different time points after grinding. Comparison of the data of Table 1 with those of Tables 2 and 3, reveals that the presence of DIA or TEM hinders crystallisation of PEG6000, resulting in lower total heats of fusion immediately after grinding (gr 0 d). The total heats of fusion at the other time points are comparable with those found in the abscence of DIA or TEM. The crystallinity (total heat of fusion) of PEG6000 (gr 0 d) was the lowest in solid dispersions containing DIA with fast cooling, followed by dispersions containing DIA with slow cooling and dispersions containing TEM. The observation that flash cooled dispersions show lower heats of fusion of PEG6000 immediately after grinding compared with slow cooled dispersions can be explained by the fast increase in viscosity during flash cooling. Furthermore, the incorporation of DIA or TEM in solid dispersions reduces the melting temperatures of all PEG6000 modifications and the formation of the extended form, but promotes the formation of the twice folded form [18].

Figure 2 and Tables 2 and 3 (data of flash-cooled dispersions; gr 0 d, gr 2 d, gr 7 d) show that amorphous PEG6000 present immediately after grinding (gr 0 d) crystallises mainly into the twice folded modification and to a small extent into the extended form. This can be easily deduced from the DSC-curves and -data of flash-cooled solid dispersions, since for flash cooled dispersions containing DIA at gr 0 d there is no integratable melting endotherm present corresponding with the twice folded form, while at gr 2 d the melting endotherm of the extended modification appears and the endotherm of the twice folded modification enlarges and becomes integratable (Fig. 2). Flash cooled dispersions containing TEM seem to undergo the same process, since at gr 2 d the melting endotherm of the twice folded form is increased compared with immediately after grinding. Tables 2 and 3, do not provide evidence that the same process takes place after grinding in slowly cooled dispersions. However, the slightly enlarging shoulder, corresponding with the twice folded modification, as observed in the DSC curves presented in Fig. 3, suggests that slowly cooled dispersions might undergo the same process after grinding, but obviously to a much lesser extent. Furthermore, the process seems to be completed 1 week after

Table 2 Peak temperatures, relative distributions of PEG6000 modifications and mass corrected total heats of fusion of PEG6000 (ΔH_f) in solid dispersions with DIA, prepared by fusion with slow (rT) or fast cooling (CO_2), determined at different time points after grinding (gr)

	$T(1)$/°C	$T(2)$/°C	$T(0)$°C	%(1)	%(2)	%(0)	ΔH_f/J g^{-1}
				DIA rT			
gr 0 d	60.10			100.00			164.81
gr 2 d	60.04			100.00			187.43
gr 7 d	60.22			100.00			185.02
gr 1 m	60.19			100.00			189.91
1 m gr 0 d	60.45			100.00			184.23
1 m gr 2 d	59.77			100.00			188.83
1 m gr 7 d	59.93			100.00			188.78
				DIA CO_2			
gr 0 d	59.58			100.00			155.08
gr 2 d	59.47	55.41		87.04	12.96		178.04
gr 7 d	60.18	57.37	62.13	77.38	22.38	0.25	186.50
gr 1 m	59.35	55.73	61.62	73.87	25.80	0.34	185.19
1 m gr 0 d	58.57	54.03	61.10	77.65	21.96	0.39	185.87
1 m gr 2 d	60.15	57.47	62.17	74.07	25.49	0.45	184.30
1 m gr 7 d	59.76	56.91	61.89	72.51	27.03	0.47	186.66

$T(1)$ is the melting temperature of the once folded modification, $T(2)$ that of the twice folded and $T(0)$ that of the extended modification.
%(1) is the relative contribution of the once folded modification to the total heat of fusion, %(2) that of the twice folded and %(0) that of the extended modification

Table 3 Peak temperatures, relative distributions of PEG6000 modifications and mass corrected total heats of fusion of PEG6000 (ΔH_f) in solid dispersions with TEM, prepared by fusion with slow (rT) or fast cooling (CO_2), determined at different time points after grinding (gr)

	$T(1)$/°C	$T(2)$/°C	$T(0)$/°C	%(1)	%(2)	%(0)	ΔH_f/J g^{-1}
			TEM rT				
gr 0 d	60.88		62.60	99.39		0.61	172.01
gr 2 d	60.17		62.03	99.51		0.50	187.11
gr 7 d	60.85		62.41	99.54		0.46	187.36
gr 1 m	59.59		61.48	99.49		0.52	185.95
1 m gr 0 d	60.97		62.41	99.50		0.50	188.28
1 m gr 2 d	59.13		61.25	99.43		0.57	185.07
1 m gr 7 d	60.86		62.30	99.46		0.56	188.33
			TEM CO_2				
gr 0 d	60.84	57.63	62.38	87.62	12.07	0.31	170.64
gr 2 d	60.58	57.19	62.26	82.13	17.49	0.39	182.10
gr 7 d	60.65	57.53	62.35	77.15	22.39	0.46	186.96
gr 1 m	59.77	55.58	61.75	76.06	23.41	0.54	182.18
1 m gr 0 d	59.90	56.03	61.88	78.99	20.69	0.32	178.60
1 m gr 2 d	59.85	55.84	61.78	77.48	22.17	0.36	181.59
1 m gr 7 d	59.05	54.26	61.21	76.82	22.80	0.39	181.19

$T(1)$ is the melting temperature of the once folded modification, $T(2)$ that of the twice folded and $T(0)$ that of the extended modification.
%(1) is the relative contribution of the once folded modification to the total heat of fusion, %(2) that of the twice folded and %(0) that of the extended modification

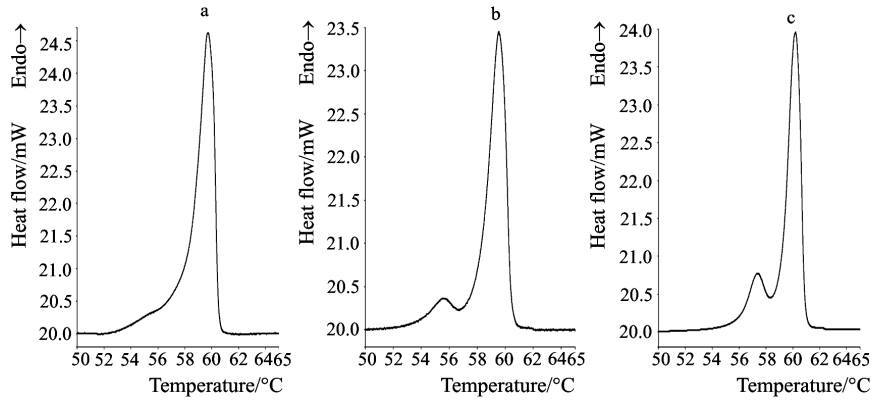

Fig. 2 DSC curves of solid dispersions, containing PEG6000 and 10% DIA, prepared by the fusion method with flash cooling, a – immediately after grinding and b – 2 or c – 7 days after grinding

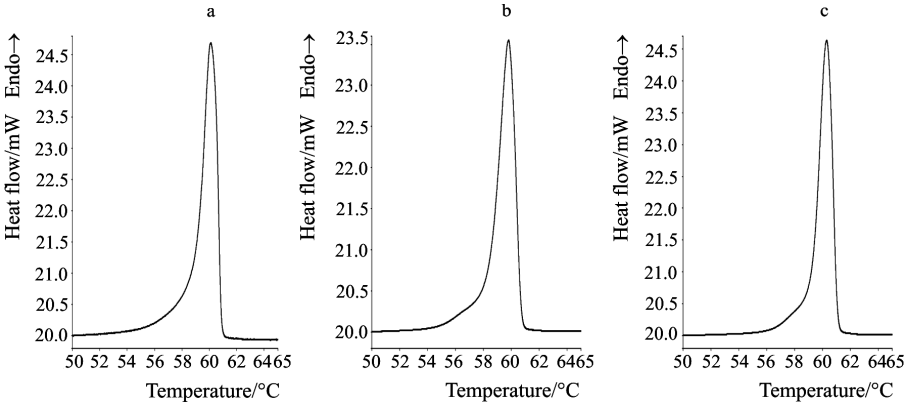

Fig. 3 DSC curves of solid dispersions, containing PEG6000 and 10% DIA, prepared by the fusion method with slow cooling, a – immediately after grinding and b – 2 or c – 7 days after grinding

grinding, since DSC-data obtained 7 days and 1 month after grinding are comparable, indicating no further crystallisation of PEG6000 during this 3-week period.

DSC data of solid dispersion slabs, kept for 1 month at 25°C and subsequently ground, sieved and analysed immediately, after 2 days and after 7 days (1 m gr 0 d, 1 m gr 2 d, 1 m gr 7 d) do not show the same crystallisation pattern after grinding. The total heats of fusion and the relative distributions of PEG6000 modifications at these time-points are comparable, suggesting that here the grinding step does not promote crystallisation of amorphous PEG6000 into the twice folded and extended modification. Moreover, the total heats of fusion and relative distributions of PEG6000 modifications are comparable with those of dispersions analysed 7 days or 1 month after grinding (gr 7 d, gr 1 m), showing that in the abscence of grinding the crystallisation process takes place in the same way and seems to be finished within 1 month.

Bragg–Brentano powder diffractometry

X-ray powder diffraction experiments were performed in order to evaluate the degree of crystallinity of the benzodiazepines incorporated in the solid dispersions at the different time points after grinding. Comparison of the X-ray powder diffraction spectra of pure drug, pure PEG6000, physical mixtures and the corresponding solid dispersions at the different time points, revealed that immediately after grinding (gr 0 d) no diffraction peaks corresponding with the benzodiazepines could be detected, irrespective of the cooling procedure applied and irrespective of the type of benzodiazepine incorporated. These observations suggest that the benzodiazepines are in a non-crystalline, amorphous state at gr 0 d. At the other time points, diffraction peaks corresponding with DIA or TEM were observed, suggesting the presence of crystalline benzodiazepine. Table 4 depicts the ratios of the intensity of a non-overlapping diffraction line of a benzodiazepine and the intensity of a non-overlapping line of PEG6000 in physical mixtures or in solid dispersions at different time points after grinding. Comparing the ratio of a solid dispersion with the ratio of the corresponding physical mixture offers the possibility to estimate the degree of crystallinity of DIA or TEM in a dispersion. No crystalline drug is present at gr 0 d. At the other time points, crystalline drug is present, but the degree of crystallinity is reduced compared with the physical mixtures.

Table 4 Ratios of the intensity of a non-overlapping diffraction line of a benzodiazepine and the intensity of a non-overlapping line of PEG6000 in a physical mixture (PM) or in solid dispersions at different time points after grinding

	DIA rT	DIA CO_2	TEM rT	TEM CO_2
PM	0.8	0.8	1.7	1.7
gr 0 d	0.0	0.0	0.0	0.0
gr 2 d	0.4	0.4	0.6	0.6
gr 7 d	0.4	0.4	0.7	0.8
gr 1 m	0.4	0.4	0.8	0.8
1 m gr 0 d	0.2	0.3	0.5	0.7
1 m gr 2 d	0.3	0.4	0.7	0.6
1 m gr 7 d	0.4	0.4	0.7	0.7

Dissolution studies

Figures 4 and 5 depict the dissolution profiles of fast and slowly cooled solid dispersions containing DIA at different time points after grinding. Comparison of the dissolution profiles after grinding (gr 0 d, gr 2 d, gr 7 d and gr 1 m) reveals that the dissolution profiles of both fast and slowly cooled dispersions deteriorate in function of time. These observations can possibly be attributed to the above discussed increase in degree of crystallinity of PEG6000 and DIA in function of time after grinding.

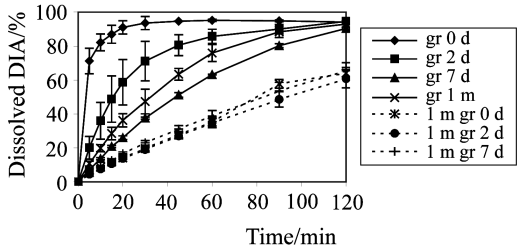

Fig. 4 Dissolution profiles of solid dispersions of DIA with PEG6000, prepared by the fusion method with fast cooling at different time points after grinding. Error bars indicate the standard deviations, *n*=3

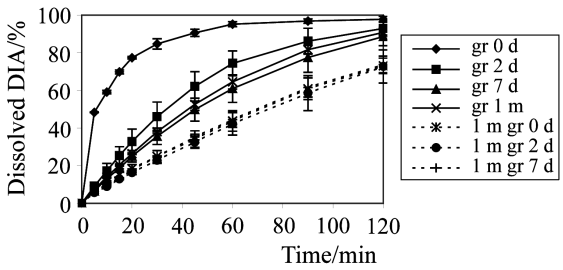

Fig. 5 Dissolution profiles of solid dispersions of DIA with PEG6000, prepared by the fusion method with slow cooling at different time points after grinding. Error bars indicate the standard deviations, *n*=3

The dissolution profiles of dispersions, kept for 1 month in the slab form and subsequently analysed at different time-points (1 m gr 0 d, 1 m gr 2 d and 1 m gr 7 d) are identical and clearly inferior compared with the dissolution profile of the ground dispersion kept for 1 month at 25°C (gr 1 m). This is especially surprising, since the degree of crystallinity of PEG6000 and the relative distributions of the different PEG6000 modifications in those dispersions are comparable and hence would suggest comparable dissolution profiles. This indicates that the difference in dissolution properties is due to the drug, and not to the polymer. Since we can exclude polymorphism of the drug [14], a plausible explanation can be found in the size of the drug particles. Indeed, in the case of ground dispersions, which are kept for 1 month in the powder form, DIA molecules can migrate throughout a dispersion particle with an approximate diameter smaller than 355 μm towards nuclei or drug crystals and crystallise, while in solid dispersions kept for 1 month in the slab form, DIA molecules can migrate from the bulk of the whole slab (a significantly larger volume) towards crystallisation sites and crystallise, resulting in larger drug crystals. Another plausible explanation is that grinding influences the nucleation-crystalgrowth process in such a way that more, but smaller drug particles are formed. Attempts to measure the actual drug particle size in the different solid dispersions using scanning electron microscopy were unsuccessful, since it was not possible to differentiate drug particles and polymer. In conclusion, particle size reduction immediately after preparation of solid dispersions containing PEG6000 will result in superior dissolution profiles compared with dispersions aged in monolith-slab form due to smaller drug crystals. These findings suggest that grinding of the solid dispersions immediately

after preparation is the preparation method of choice instead of liquid filling of hard gelatin capsules resulting in monolith-plugs.

Figures 6 and 7 show the dissolution profiles of fast and slowly cooled solid dispersions containing TEM at different time points after grinding. Comparison of the dissolution profiles after grinding (gr 0 d, gr 2 d, gr 7 d and gr 1 m) reveals that the dissolution profiles of both fast and slowly cooled dispersions are comparable and do not deteriorate in function of time after grinding as observed for DIA. The dissolution profiles of dispersions, kept for 1 month in the slab form and subsequently ground and analysed at different time-points (1 m gr 0 d, 1 m gr 2 d and 1 m gr 7 d) are identical and clearly inferior compared with the dissolution profiles of the ground dispersion kept for 1 month at 25°C (gr 1 m). The mechanism behind these inferior dissolution profiles and consequences towards preparation of dispersions containing PEG6000 are thought to be identical with those discussed above.

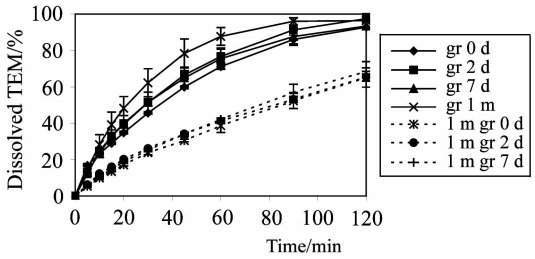

Fig. 6 Dissolution profiles of solid dispersions of TEM with PEG6000, prepared by the fusion method with fast cooling at different time points after grinding. Error bars indicate the standard deviations, *n*=3

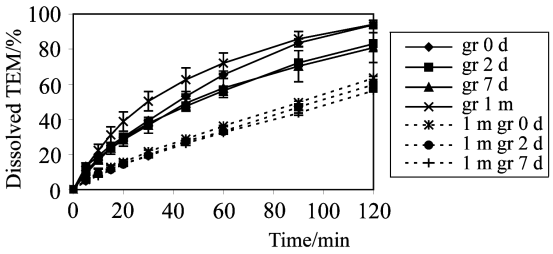

Fig. 7 Dissolution profiles of solid dispersions of TEM with PEG6000, prepared by the fusion method with slow cooling at different time points after grinding. Error bars indicate the standard deviations, *n*=3

Figure 8 shows the dissolution profiles of solid dispersion tablets containing TEM at different time-points after preparation. These tablets were without any grinding introduced in the dissolution medium. Again, the dissolution profiles deteriorate in function of time. The dissolution profiles of tablets containing DIA show the same tendency, but less pronounced. The observed change in dissolution profiles in function of time can most probably be attributed to an increase in degree of crystallinity of drug and PEG6000 and an increase in drug particle size.

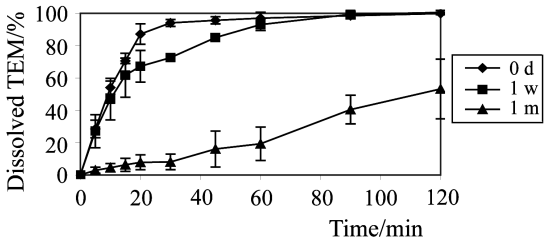

Fig. 8 Dissolution profiles of solid dispersion tablets containing TEM and PEG6000 immediately (0 d), 1 week (1 w) and 1 month (1 m) after preparation. Error bars indicate the standard deviations, n=3

Conclusions

Grinding solid dispersions immediately after solid dispersion preparation results in superior dissolution properties compared with solid dispersions kept in the monolith-slab form and subsequently ground. These findings suggest that grinding of solid dispersions immediately after preparation is the preparation method of choice instead of liquid filling of hard gelatin capsules resulting in monolith-plugs.

References

1 W. L. Chiou and S. Riegelman, J. Pharm. Sci., 60 (1971) 1281.
2 C. Leuner and J. Dressman, Eur. J. Pharm., 50 (2000) 47.
3 J. L. Ford, Pharm. Acta Helv., 61 (1986) 69.
4 D. Q. M. Craig, Int. J. Pharm., 231 (2002) 131.
5 M. Bhattacharyya, S. K. Basu, B. K. Gupta, S. K. Ghosal, S. C. Mandal and S. C. Chattaraj, Drug Dev. Ind. Pharm., 19 (1993) 739.
6 F. Fawaz, F. Bonini, M. Guyot, J. Bildet, M. Maury and A. M. Lagueny, Int. J. Pharm., 132 (1996) 271.
7 G. Trapani, M. Franco, A. Latrofa, M. R. Pantaleo, M. R. Provenzano, E. Sanna, E. Maciocco and G. Liso, Int. J. Pharm., 184 (1999) 121.
8 N. Zerrouk, C. Chemtob, P. Arnaud, S. Toscani and J. Dugue, Int. J. Pharm., 225 (2001) 49.
9 S. K. Dordunoo, J. L. Ford and M. H. Rubinstein, Drug Dev. Ind. Pharm., 17 (1991) 1685.
10 S. K. Dordunoo, J. L. Ford and M. H. Rubinstein, J. Pharm. Pharmacol., 49 (1997) 390.
11 J. L. Ford and M. H. Rubinstein, Pharm. Acta Helv., 54 (1979) 353.
12 J. L. Ford and M. H. Rubinstein, Pharm. Acta Helv., 55 (1980) 1.
13 E. S. Saers, C. Nystrom and M. Alden, Int. J. Pharm., 90 (1993) 105.
14 S. Verheyen, N. Blaton, R. Kinget and G. Van den Mooter, Int. J. Pharm., 249 (2002) 45.
15 S. Verheyen, N. Blaton, R. Kinget and G. Van den Mooter, (2002) submitted.
16 C. P. Buckley and A. J. Kovacs, Progr. Colloid & Polymer Sci., 58 (1975) 44.
17 C. P. Buckley and A. J. Kovacs, Colloid & Polymer Sci., 254 (1976) 695.
18 S. Verheyen, P. Augustijns, R. Kinget and G. Van den Mooter, Thermochim. Acta, 380 (2001) 153.
19 G. A. Saleki, C. Ahlneck and G. Zografi, Int. J. Pharm., 101 (1994) 237.
20 G. Van den Mooter, J. Van den Brande, P. Augustijns and R. Kinget, J. Therm. Anal. Cal., 57 (1999) 493.