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

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## Abstract

Differential scanning calorimetry (DSC) data showed that the crystallinity of poly(ethylene glycol) 6000 in solid dispersions containing and diazepam or temazepam only slightly increased upon aging and that the twice folded modification of the polymer unfolded into the once folded modification during aging, while the once folded modification did not unfold. This unfolding was found to be time and temperature dependent. X-ray powder diffraction data revealed that the drug crystallinity in the solid dispersions slightly increased upon aging. The dissolution profiles of aged and non-aged solid dispersions were comparable. It was concluded that polymer unfolding did not have an impact on the pharmaceutical performance of the investigated dispersions.

**Keywords:** DSC, dissolution, poly(ethylene glycol), polymer unfolding, solid dispersion, X-ray powder diffraction

## Introduction

A significant number of 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 studied to increase aqueous solubility/dissolution rate, the formulation of solid dispersions is still one of the most popular ones [1, 2]. Mechanisms responsible for the improved aqueous solubility/dissolution properties of solid dispersions include reduction 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].

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Despite the potential of solid dispersion formulations containing poly(ethylene glycol) (PEG) to improve the oral bioavailability of drugs [5–8], only few products have been commercialized, probably because of production issues and/or the physical instability of solid dispersions resulting in changing dissolution profiles during aging [9–13]. Physical changes possibly responsible for changing dissolution properties upon aging include a) increase in the degree of crystallinity of drug or poly(ethylene glycol) by crystal improvement or by crystallisation of amorphous drug or polymer, b) polymorphic conversion of drug or polymer, c) increase in drug particle size due to Ostwald ripening or crystallisation of amorphous drug upon present drug crystals.

PEG6000 crystallizes forming lamellae with chains either fully extended (0) or folded once (1) or twice (2) [14, 15]. The twice folded modification has a lower melting temperature with respect to the once folded, the melting temperature of the once folded modification is lower than that of the extended form (Fig. 1).

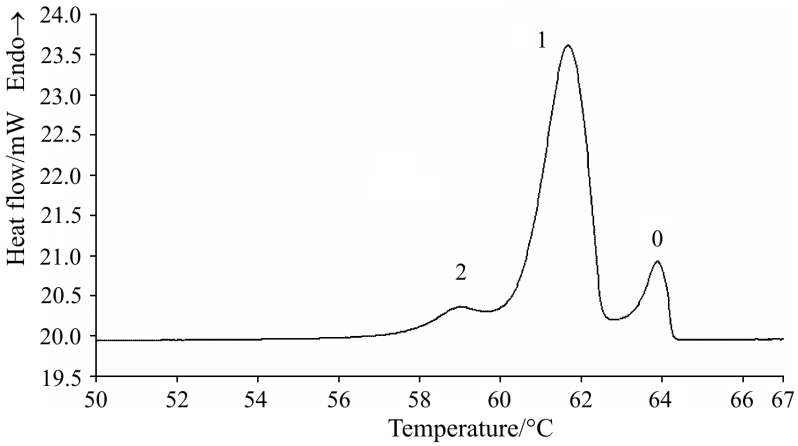


**Fig. 1** DSC-curve of PEG6000 showing melting endotherms of three polymorphic forms. 2 – twice folded; 1 – once folded; 0 – extended. Endothermic signals are plotted upwards

Throughout the years, several authors, investigating solid dispersions containing PEG4000 or PEG6000 as carrier material, reported DSC-curves of the melting of PEG showing a shoulder on the leading edge of the main melting endotherm or overlapping endotherms, and they assigned these phenomena to the presence of the once folded modification (the lower melting peak or shoulder) together with the extended modification (the higher melting peak) of PEG [8, 11, 12, 16–19]. These authors investigated solid dispersions containing PEG4000 or PEG6000 using conventional DSC at a rather high heating rate (4–10°C $min^{-1}$) resulting in a poor resolution often not capable of separating the melting endotherms corresponding to the different forms of PEG. Furthermore, the melting endotherm of PEG6000 at 61°C was often wrongly assigned to melting of the extended modification instead of melting of the once folded modification and also the shoulder or endotherm at 55–59°C was often wrongly assigned to melting of the once folded modification instead of melting of the twice folded modifi-

cation. Folded modifications of PEG are known to unfold during annealing and this unfolding or crystal thickening is found to increase with annealing temperature and time [15, 20]. The latter authors showed, varying the heating rate (0.5 to 8°C $min^{-1}$), that during DSC-analysis of PEG4000 molten once folded PEG4000 recrystallizes (crystal thickening) forming extended PEG4000. In other words during DSC-analysis the once folded modification of PEG4000 unfolds into the extended modification. This unfolding was found to be related with the heating rate applied. The slower the heating rate, the more extended PEG4000 was formed.

Analyzing at a low heating rate (0.5 to 2°C $min^{-1}$) improves the resolution but results thus in an overestimation of the extended PEG4000 present due to crystal thickening during analysis, while using a higher heating rate (4–20°C $min^{-1}$) results in a low resolution often not capable of separating the melting endotherms of the once folded and the extended form of PEG4000. In contrast, PEG6000 does not show substantial unfolding of the once folded into the extended modification during analysis using a heating rate of 1°C $min^{-1}$ [14, 21, 22]. Moreover, we showed by varying the heating rate and measuring the relative enthalpies of fusion corresponding to the different PEG6000 forms, that the twice folded modification is sufficiently stable during DSC-analysis at 1°C $min^{-1}$ and differential scanning calorimetry (DSC) using a heating rate of 1°C $min^{-1}$ was proposed as an interesting tool to investigate the presence of the different modifications of PEG6000 in solid dispersions [22]. In addition, we also observed that the preparation method used, type and concentration of drug incorporated in the dispersions had a significant influence on the formation of the folded and extended modifications of PEG6000 in solid dispersions. In a second report, these dispersions containing PEG6000 and diazepam (dia) or temazepam (tem), were physically characterized in order to unravel the mechanism of increased dissolution of dia and tem in the presence of PEG6000 [23].

The purpose of the present study was to evaluate the influence of aging upon the physical structure of these solid dispersions and to characterize the nature and mechanism of any aging process using DSC and X-ray powder diffraction.

## Materials and methods

### *Materials*

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

### *Preparation of physical mixtures*

Physical mixtures, containing 5, 10, 20 and 40 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.

*Preparation of solid dispersions by the fusion method*

Solid dispersions containing 0, 5, 10, 20 and 40 mass/mass% of 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 10 min cooled either at room temperature or by placing the closed container for 15 min in a mixture of solid carbon dioxide and acetone (fast cooling). Subsequently, the solid dispersions were stored in vacuo over $P_2O_5$ for 72 h.

*Preparation of solid dispersions by the solvent evaporation method*

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

All dispersions were pulverized with mortar and pestle, sieved (<355 μm) and dried in vacuo over $P_2O_5$ for at least 48 h. Dispersions were stored at 6 or 25°C in sealed glass bottles and analyzed immediately after the second drying step, after 6 months and after 12 months.

*Thermal analysis*

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 in aluminium pans (TA instruments, Brussels, Belgium), hermetically sealed and subsequently scanned at 1°C $min^{-1}$ under nitrogen gas purge (20 mL $min^{-1}$). 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).

In order to evaluate the presence of residual solvent in the solid dispersions prepared by the solvent evaporation method, samples (4–6 mg) were placed in open pans and heated under nitrogen purge (20 mL $min^{-1}$) from room temperature to 120 (dia) or 150°C (tem) at 20°C $min^{-1}$. Subsequently, the samples were kept isothermally during 3 min at these end temperatures. Comparison of the masses before and after the assessment of the temperature program, revealed that the mass loss was always less than 0.5%.

*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 $CuK_\alpha$ radiation ($\lambda$=1.54184 Å) was Ni filtered. Diverging and anti-scattering slits were set at 1°, the receiving slit at 0.2 mm. Tube voltage and tube current were 40 kV and 40 mA, respectively and the diffraction patterns were collected in the angular range $5°<2\theta<60°$ in step scan mode (step interval 0.02°, counting time 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.

*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 demineralized water at 37°C). At designated time intervals, 1.0 mL samples were withdrawn, filtered (0.20 μm), analyzed by HPLC and replaced by the same amount of fresh dissolution medium. The dissolution experiments were performed in triplicate. Dissolution profiles were statistically compared using a paired *t*-test. A difference was considered to be statistically significant when $p<0.05$.

Concentrations of dia and tem were determined using an isocratic HPLC method on a HPLC system equipped with a L-7100 Lachrom pump, a L-7400 Lachrom UV-detector, a L-7200 Lachrom autosampler and a D-7000 interface (all from Merck-Hitachi, Darmstadt, Germany). The column used was a LiChrospher 60 RP Select B (125×4 mm, 5 μm) (Merck, Darmstadt, Germany), the flow rate amounted to 1 mL $min^{-1}$ and the volume injected 20 μL. The mobile phase consisted of acetonitrile and a phosphate buffer (pH 5.5; 0.05 M containing 0.03 M of triethylamine). The detector wavelength was set at 230 nm. The ratio of acetonitrile to buffer (*v/v*) was 45/55 for dia and 42/58 for tem. The relative standard deviations of the interday and intraday variabilities amounted to less than 3% ($n$=7) and less than 2% ($n$=6), respectively.

## Results and discussion

The folding behavior of PEG6000 can be qualitatively and quantitatively evaluated by a high resolution DSC-method [22]. The chain-folded modifications of PEG6000 are less stable than the extended form and tend to unfold. This unfolding may have an influence on the pharmaceutical performance and stability of solid dispersions containing PEG6000 as carrier material. Besides detection of folding/unfolding, DSC offers the possibility to evaluate the enthalpy of fusion of PEG6000 in the solid dispersions, which is a measure of the degree of crystallinity of the polymer. 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 melted PEG6000 during DSC-analysis 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 (see below).

Aging solvent-treated PEG6000, heat-treated PEG6000 and solid dispersions containing dia or tem for 12 months at 25°C resulted in a small increase of the total enthalpy of fusion of PEG6000 (increases were mostly less than 5%), aging for 12 months at 6°C resulted in even minor increases of the total enthalpy of fusion of PEG6000. Since the enthalpy of fusion is a measure of the degree of crystallinity, it can be concluded that the crystallinity of PEG6000 both in solid dispersions and solvent- or heat-treated samples only slightly increases upon aging.

Figures 2 and 3 depict the DSC-curves of solid dispersions consisting of PEG6000 and 40% dia, prepared by the solvent method and the fusion method with fast cooling, aged for 0, 6 and 12 months at 25°C. These DSC-curves clearly show the influence of aging at 25°C upon the melting behaviour of PEG6000. The peak temperature of the twice-folded PEG6000 modification increases slightly towards that of the once-folded modification, and the endothermic melting peak of the twice-folded modification merges gradually with that of the once folded modification during aging at 25°C. Solvent- or heat-treated PEG6000 and solid dispersions containing dia or tem, which possess the twice-folded modification all undergo this gradual unfolding of the twice-folded to the once-folded form of PEG6000 during aging at 25°C.

The once-folded PEG6000 modification can also unfold to the more stable extended form [14, 15]. The obtained DSC-data, however, show that aging at 6 or 25°C for 12 months does not result in unfolding of the once-folded to the extended

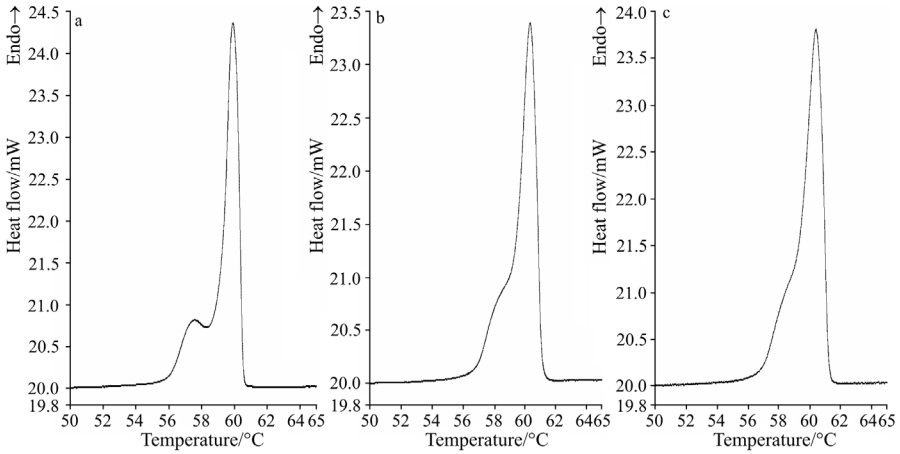


**Fig. 2** DSC-curves of solid dispersions, containing PEG6000 and 40% dia, prepared by the solvent evaporation method and aged at 25°C for a – 0, b – 6 and c – 12 months. Endothermic signals are plotted upwards

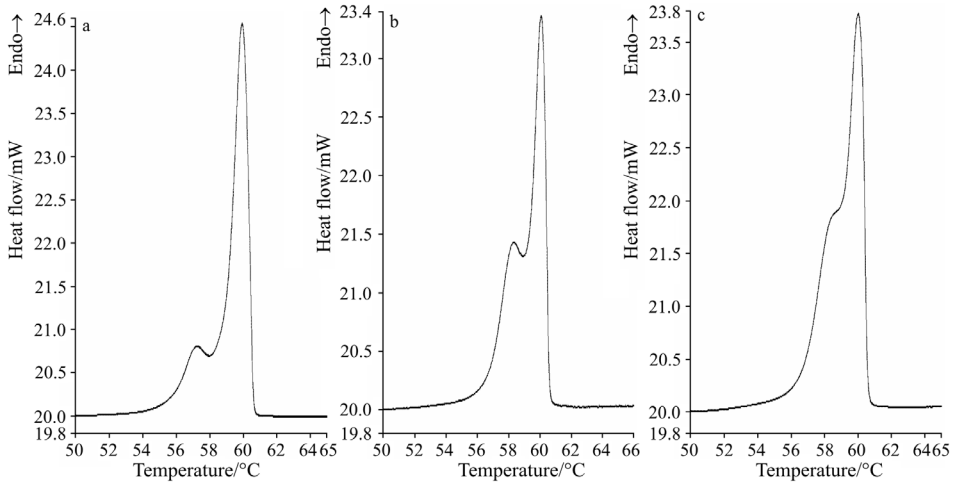


**Fig. 3** DSC-curves of solid dispersions, containing PEG6000 and 40% dia, prepared by the fusion method with fast cooling and aged at 25°C for a – 0, b – 6 and c – 12 months. Endothermic signals are plotted upwards

form. Aging at 6°C results also in conversion of the twice-folded to the once-folded modification of PEG6000 but obviously to a lesser extent than during aging at 25°C. These observations suggest that the rate of unfolding of the twice-folded to the once-folded and probably also the unfolding of the once-folded to the extended form are temperature and time dependent. Furthermore, the presented DSC-curves highlight the potential of the used DSC-method to qualitatively evaluate the chain behaviour of PEG6000.

Comparison of the X-ray powder diffraction spectra of physical mixtures and the corresponding non-aged solid dispersions, revealed the abscence of formation of polymorphic crystal forms of the benzodiazepines during solid dispersion preparation and also that the crystallinity of the drug was reduced, whether dia or tem was incorporated and irrespective of the solid dispersion preparation method used [23]. This reduction in crystallinity can be attributed to the formation of imperfect drug crystals and/or partially transformation of the drug into the amorphous state during solid dispersion preparation. On the other hand, preferential orientation could be responsible for the apparent higher drug crystallinity in physical mixtures compared with unaged solid dispersions. Furthermore, the fact that PEG6000 may cover the drug particles in the solid dispersions must be considered as well. In this case the drug particles will interfere in a different way with the entering X-ray beams compared with the non-PEG6000 covered drug particles of the physical mixtures (matrix absorption effect).

Possible crystallisation of the amorphous drug fraction and crystal improvement during aging of the solid dispersions will result in increasing intensities of the drug X-ray diffraction lines.

Table 1 depicts the degrees of crystallinity of dia in physical mixtures or in aged and non-aged solid dispersions. Comparison of the values of aged and non-aged dis-

persions reveals that the crystallinity of the incorporated diazepam tends to increase upon aging for 12 months at 6 or 25°C. Comparison of the values of dispersions aged for 12 months at 6 or 25°C, reveals that storage of solid dispersions at 6°C does not substantially retard crystallisation of diazepam compared with dispersions stored at 25°C. The same tendencies were observed for dispersions containing tem.

**Table 1** Degrees of crystallinity expressed as fraction of the initial value of dia in physical mixtures (PM) and in aged and non-aged solid dispersions prepared by the solvent method ($CH_2Cl_2$), the fusion method with fast (Fu $CO_2$) or slow (Fu rT) cooling

| Dia | 5% | 10% | 20% | 40% |
|---|---|---|---|---|
| | | PM | | |
| | 1.0 | 1.0 | 1.0 | 1.0 |
| | | $CH_2Cl_2$ | | |
| 0 m | 0.2 | 0.4 | 0.8 | 0.9 |
| 12 m 25°C | 0.3 | 0.5 | 0.6 | 0.6 |
| 12 m 6°C | 0.3 | 0.4 | 0.7 | 0.7 |
| | | Fu $CO_2$ | | |
| 0 m | 0.2 | 0.4 | 0.5 | 0.8 |
| 12 m 25°C | 0.3 | 0.6 | 0.7 | 1.0 |
| 12 m 6°C | 0.3 | 0.5 | 0.8 | 0.9 |
| | | Fu rT | | |
| 0 m | 0.2 | 0.3 | 0.6 | 0.5 |
| 12 m 25°C | 0.3 | 0.6 | 1.0 | 0.6 |
| 12 m 6°C | 0.3 | 0.5 | 0.8 | 0.7 |

Figures 4 and 5 show dissolution profiles of solid dispersions aged for 0 and 12 months at 25°C, containing dia or tem and prepared by the solvent evaporation method or the fusion method with fast cooling. The dissolution profiles of solid dispersions containing dia or tem, prepared by the fusion method with fast cooling and aged for 12 months at 6 or 25°C were not significantly different from the dissolution profiles of the corresponding non-aged dispersions. The same was true for dispersions containing dia and tem prepared by the fusion method with slow cooling (data not shown). The dissolution profiles of solid dispersions containing 5, 10 or 20 mass/mass% dia or tem, prepared by the solvent method and aged for 12 months at 6 or 25°C were not significantly different from the profiles of the corresponding non-aged dispersions. However, the dissolution profiles of non-aged dispersions, containing 40 mass/mass% dia, prepared by the solvent method were significantly better than the profiles of dispersions aged for 12 months, while non-aged dispersions containing 40 mass/mass% tem, prepared by the solvent method were significantly inferior compared with the corresponding profiles of dispersions aged for 12 months. Thus, besides the latter exceptions, aging, and more spe-

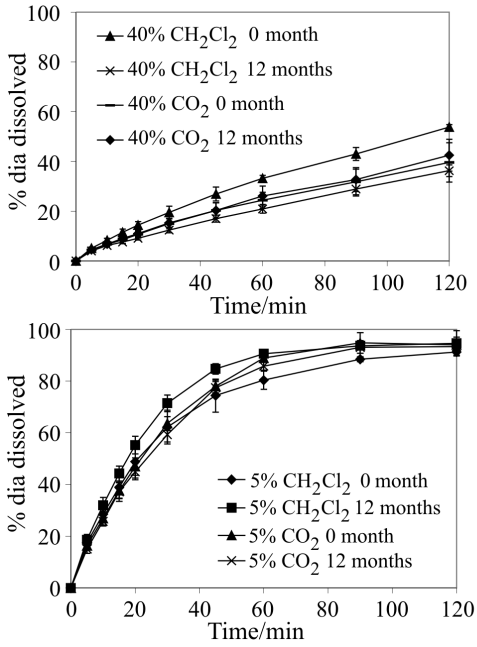


**Fig. 4** Dissolution profiles of solid dispersions of dia with PEG6000, prepared by the solvent evaporation method ($CH_2Cl_2$) and the fusion method with fast cooling ($CO_2$), aged for 0 and 12 months at 25°C The percentages represent dia in PEG6000 by mass. Error bars indicate the standard deviations, $n$=3

cific, the time-periods and temperatures applied, do not seem to have a significant influence on the dissolution performance of the solid dispersions investigated.

Hence, unfolding of the twice folded modification of PEG6000 into the once folded modification as well as the slight increase in enthalpy of fusion of PEG6000 during aging and the observation that the crystallinity of dia and tem tend to increase upon aging did not have a substantial influence on the dissolution profiles of most of the investigated solid dispersions (making abstraction of the above mentioned exceptions).

How might unfolding or crystal thickening during aging have an impact on the dissolution performances of solid dispersions?

- the dissolution rate of PEG6000 might substantially differ depending on the amounts twice folded, once folded and extended modification present. However, since the total enthalpies of fusion of non-aged or aged for 12 months at 25°C pure PEG6000 samples, prepared or treated by the solvent method or the fusion method with fast cooling, do not much differ although the unaged samples contain much more twice folded modification than the aged samples, one might expect that the influence of the presence of different amounts of the different forms of PEG6000, due to crystal thickening, on the dissolution rate of PEG6000 will be negligibly small. On the other hand, PEG6000 with a low degree of crystallinity will have a higher dissolution rate than highly crystalline PEG6000.

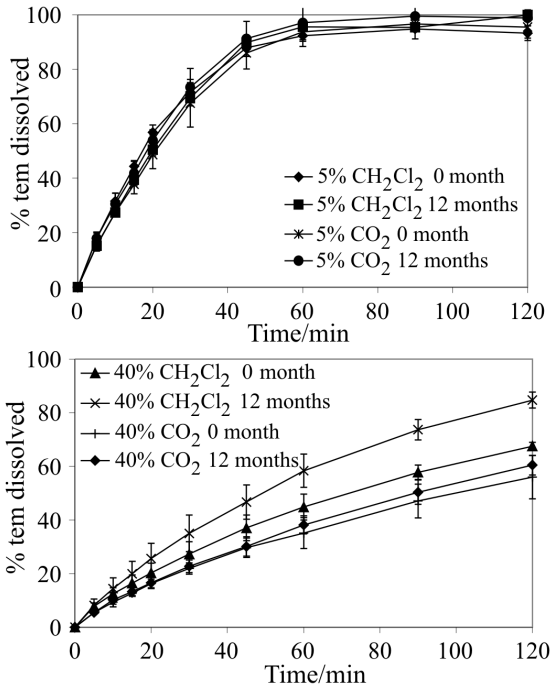


**Fig. 5** Dissolution profiles of solid dispersions of tem with PEG6000, prepared by the solvent evaporation method ($CH_2Cl_2$) and the fusion method with fast cooling ($CO_2$), aged for 0 and 12 months at 25°C. The percentages represent tem in PEG6000 by mass. Error bars indicate the standard deviations, $n$=3

- unfolding or crystal thickening involves a reorganisation of the PEG6000 molecules in the PEG6000 crystals. This reorganisation might have an influence on the stability of the amorphous drug fraction and amorphous regions consisting of a molecular dispersion of PEG6000 and drug by triggering recrystallisation. However, the drug crystallinity in the investigated solid dispersions showed only a slight increase upon aging for 12 months at both 6 and 25°C.

Ostwald ripening, a process whereby small particles dissolve and subsequently precipitate upon the large particles resulting in coarser drug particles and hence reduced dissolution, does not seem to appear or to a small (negligible) extent under the aging conditions applied, since the dissolution profiles of aged and non-aged solid dispersions are comparable.

The absence of any aging effect upon the dissolution profiles is in agreement with previous reports [5, 24–28], but disagrees with the results of several other authors, who reported changing dissolution profiles of solid dispersions during aging [9–13].

Our observations suggest that drug (dia or tem) and PEG6000, predominantly recrystallize in the time-interval between preparation and the first analysis, and to a small extent during additional aging for 12 months at 6 or 25°C. It is obvious that if the first analysis of the solid dispersions was performed closer to or immediately after

solid dispersion preparation, recrystallisation of dia, tem or PEG6000 possibly was not completed, resulting in an amorphous drug and polymer fraction responsible for superior dissolution profiles, which would change upon aging due to recrystallisation of the remaining amorphous fractions.

## Conclusions

DSC-analysis revealed that the twice folded modification of PEG6000 converts into the once folded modification during aging. This unfolding was found to be temperature and time dependent. Crystal thickening of PEG6000 was found to have a negligible impact on the dissolution properties of the investigated solid dispersions. The dissolution profiles of aged and non-aged solid dispersions were comparable, irrespective of the preparation method used and independent of the type of drug (dia or tem) incorporated. X-ray powder diffraction data revealed, that the drug crystallinity in the solid dispersions slightly increased upon aging and DSC data showed that the crystallinity of PEG6000 slightly increased upon aging. These observations suggest that the drug (dia or tem) and PEG6000, predominantly recrystallize in the time interval between preparation and the first analysis and to a small extent during additional aging for 12 months at 6 or 25°C.

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