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Research paper

The influence of povidone K17 on the storage stability of solid dispersions of nimodipine and polyethylene glycol

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Abstract

Previous studies revealed that solid dispersions containing nimodipine and polyethylene glycol 2000 can be effectively prevented from recrystallization by adding povidone K17. These systems are characterized by a high dissolution rate and a remarkable supersaturation of the drug in the dissolution media. It is still unknown if these characteristics are achievable with all polyethylene glycol and povidone mixtures. The objective of the present study is to find out, whether povidone K17 has to be dissolved in melted polyethylene glycol during the preparation process of solid dispersions by the melting method in order to avoid recrystallization of the drug and to ensure storage stability. Solid dispersions consisting of 20% (m/m) nimodipine, 16% (m/m) povidone K17 and 64% (m/m) of six different mixtures of polyethylene glycol 2000 and 8000 were prepared by the melting method and investigated by dissolution testing, thermal analysis and X-ray diffraction. As the solubility of povidone K17 in polyethylene glycol 2000 is about 70% at 65 °C and decreases with increasing molecular weight of the polyethylene glycol, mixtures containing different amounts of dissolved povidone K17 are obtained by varying the mixing ratio of polyethylene glycol 2000 and 8000. Recrystallization is inhibited in the formulations, containing mainly polyethylene glycol 2000 whereas recrystallization occurs in systems consisting predominantly of polyethylene glycol 8000. These results show clearly that dissolution of povidone in melted polyethylene glycol is a prerequisite in order to prevent recrystallization.

Keywords: Dissolution; Nimodipine; Polyethylene glycol; Povidone; Recrystallization; Solid dispersions; Supersaturation; Stability

1. Introduction

The poor solubility of drug substances in water and the aqueous gastro-intestinal fluids leads often to low dissolution rates and thus to insufficient bioavailability. There are several possibilities to enhance the dissolution rate, like micronization, enhancing the wettability or incorporating the drug in a hydrophilic carrier material obtaining products called solid dispersions. Depending on the properties of the respective substances and the preparation process the product is either a solid suspension or a solid solution [1–3].

Solid dispersions often show an enhanced solubility because of the transformation of the drug's crystal lattice, a reduction of particle size and a better wettability exerted by the hydrophilic carrier.

Solid solutions can be oversaturated resulting in a thermodynamically unstable system which is prone to convert into a more stable state by recrystallization [4]. One proven method to avoid recrystallization is the addition of excipients being able to increase the viscosity of the system and to enclose dissolved drug molecules inhibiting the contact to other molecules of the active.

Previous studies on solid dispersions without recrystallization inhibitor containing 20% (m/m) of nimodipine and 80% (m/m) of polyethylene glycol 2000 prepared by the

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melting method have been reported to show ageing phenomena depending on preparation and storage conditions [5].

In comparison with that, solid dispersions containing 20% (m/m) of nimodipine, 16% (m/m) of povidone K17 and 64% (m/m) of polyethylene glycol 2000 showed a good storage stability maintaining desired properties like fast dissolution rate with high supersaturation [6].

It is still open, which povidone/polyethylene glycol compositions and ratios work successfully preventing recrystallization. Also, it is unclear up to now, whether povidone K17 has to be dissolved in melted polyethylene glycol during the preparation process of solid dispersions by the melting method in order to avoid recrystallization of the drug thereby ensuring storage stability.

Suzuki and Sunada [7] attributed the lack of recrystallization inhibition of nifedipine in solid dispersions containing the drug, polyethylene glycol 6000 and hydroxypropylmethylcellulose, to the fact that hydroxypropylmethylcellulose could not be dissolved in the melted polyethylene glycol 6000. The miscibility of the recrystallization inhibiting compound with the carrier is described by Suzuki and Sunada [8] as a prerequisite for the recrystallization inhibiting effect of povidone, polyvinylalcohol and pullulan as recrystallization inhibitors in combination with nicotinamide as carrier.

Therefore, the objective of the present study is to find out, if there is a correlation between the amount of dissolved povidone in melted polyethylene glycol and the stability of the solid dispersion.

2. Materials and methods

2.1. Materials

Nimodipine (Ph. Eur., 5th edition 2005) was provided by Alfred E. Tiefenbacher GmbH & Co. KG, D-Berlin. Polyethylene glycol 2000 and polyethylene glycol 8000 (Macrogole Ph. Eur., 5th edition 2005) were given by Clariant GmbH, D-Burgkirchen. Povidone K17 (Povidone, Ph. Eur., 5th edition 2005) was received from BASF AG, D-Ludwigshafen.

2.2. Methods

2.2.1. Determination of the solubility of povidone K17 in polyethylene glycols at 65 °C

Samples containing 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80% (m/m) of povidone K17 were prepared by intimately mixing povidone K17 with melted polyethylene glycols of different molecular weights (polyethylene glycol 1000, 1500, 2000 and 3000) using mortar and pestle. The mixtures were kept in vials for 2 weeks at +65 °C. After this time, it was determined macroscopically, whether povidone K17 was dissolved or still suspended in polyethylene glycol.

2.2.2. Preparation and storage of solid dispersions containing 20% (m/m) of nimodipine, 16% (m/m) of povidone K17 and 64% (m/m) of different mixtures of polyethylene glycol 2000 and 8000

Solid dispersions containing 20% (m/m) of nimodipine, 16% (m/m) of povidone K17 and 64% (m/m) of polyethylene glycol 2000 and/or polyethylene glycol 8000 were prepared by heating the various polyethylene glycol mixtures at 85 °C. After melting was completed, nimodipine was added, the temperature was increased to 95 °C and the mixture was stirred every half an hour until the drug was dissolved completely in the melt and a homogeneous solution was obtained. The temperature was lowered to 85 °C, povidone K17 was added and the mixture was stirred every half an hour until dissolution of povidone K17 in formulation 1 was complete. Then immediately all formulations were poured into tablet moulds, which had a temperature of 65 °C. The dispersions were then kept at 25 °C over silica gel. After an overall storage period of 1 day, 1 week or 4 weeks, solid dispersions were investigated by dissolution testing, thermal analysis, X-ray diffraction, hot-stage microscopy. The compositions of the formulations are given in Table 1.

2.2.3. Dissolution studies

A paddle apparatus (DT 6 R, ERWEKA, D-Heusenstamm) according to Ph. Eur., 5th edition 2005 was used for dissolution studies. The dissolution testing was carried out at a temperature of 37 ± 0.5 °C and a stirring rate of 150 rpm in 1000 ml of distilled water. Samples were withdrawn every 3 min. The nimodipine concentration was determined spectrophotometrically in flow-through cells (Lambda-2-Spectrometer, Perkin-Elmer, D-Überlingen) at $\lambda = 362$ nm. The area accessible for the dissolution medium was limited by the area of the opening of the tablet mould and was kept constant during the dissolution test at 38.48 mm^2 (equivalent to the diameter of 7 mm of the tablet mould).

2.2.4. X-ray diffraction

The extent of crystallinity in solid dispersions was examined using an X-ray goniometer (Rigaku, J-Tokyo). The scanning rate was adjusted to 2°/min. Samples were prepared by pouring the melt directly into special frames designed for X-ray analysis, which had a temperature of 65 °C.

Table 1
Composition of the different formulations

	Nimodipine (%)	PVP K17 (%)	PEG 2000 (%)	PEG 8000 (%)
Formulation 1	20	16	64	0
Formulation 2	20	16	51.2	12.8
Formulation 3	20	16	38.4	25.6
Formulation 4	20	16	25.6	38.4
Formulation 5	20	16	12.8	51.2
Formulation 6	20	16	0	64

2.2.5. Differential scanning calorimetry (DSC)

Thermal investigations were performed using a DSC 821^e (Mettler-Toledo AG, D-Gießen). The temperature ranged from −20 to +170 °C with a heating rate of 10 K/min. Experiments were carried out in aluminium pans of 40 μl volume with a pierced lid. The nitrogen flow rate was adjusted to 50 ml/min. Sample preparation was done by cutting slides of an appropriate weight of the tablets prepared as described in 2.2.1 using a razor blade. The slides were brought into contact with the aluminium pan by pushing it carefully onto the bottom of the pan with a glass rod thereby ensuring the contact between pan and slide over the entire lower surface of the slide. DSC traces shown in Figs. 12 and 13 are standardized to a sample weight containing 9.6 mg polyethylene glycol. DSC traces of the polyethylene glycols of Fig. 14 are standardized to 9.6 mg sample weight and thermograms of nimodipine to 3.0 mg.

2.2.6. Hot stage microscopy (HSM)

Microscopic observations were carried out using a thermomicroscope with polarisation equipment (Thermovar HT 1 B11, C. Reichert AG, A-Wien). The temperature ranged from 20 to 170 °C with a heating rate of approximately 20 °C/min. Sample preparation was done by cutting a slide of an appropriate size of the tablets prepared as described in 2.2.1 using a razor blade.

3. Results and discussion

Previous studies reported that solid dispersions containing crystalline nimodipine show a slow dissolution rate with a saturation concentration of 3–4 mg/L, whereas solid dispersions containing dissolved nimodipine are characterized by a fast dissolution rate and a remarkable supersaturation [5]. Preventing the drug from recrystallization by adding povidone K17 has shown to be successful [6]. The objective of the present study is to find out, whether povidone K17 has to be dissolved in melted polyethylene glycol during the preparation process of solid dispersions by the melting method in order to ensure that recrystallization of the drug be inhibited.

To get formulations with various amounts of povidone K17 dissolved in melted polyethylene glycol, the ratio of polyethylene glycol 2000 to polyethylene glycol 8000 has been varied. Six formulations have been prepared. The amount of polyethylene glycol 8000 has been increased from 0% to 100% in steps of 20% (Table 1). The solubility of povidone K17 in polyethylene glycol decreases by increasing the molecular weight of polyethylene glycol. Up to polyethylene glycol 2000 the solubility of povidone K17 amounts to 70% at 65 °C, from polyethylene glycol 3000 it drops below 5% at 65 °C (Table 2). In order to lower the solubility even more, polyethylene glycol 8000 was used.

Dissolution studies are an important tool to characterize solid dispersions. Samples were investigated after 1 day, 1 week and 4 weeks of storage at 25 °C over silica gel. After 1 day, formulations 1–3 show a high dissolution rate with about sixfold supersaturation. Formulations 4–6 liberate slowly without supersaturation in one batch, whereas the other two batches exhibit a fast dissolution with high supersaturation. This may be explained with the fact that recrystallization is a spontaneous process not progressing equivalently fast in all samples. Nevertheless, this shows that recrystallization could not be inhibited adequately in formulations 4–6. Due to the described inconsistency especially in formulations 4–6, the results of the dissolution testing after 1 day of storage are not shown and investigations have been repeated after 1 week of storage.

Table 2
Solubility of povidone K17 in polyethylene glycol

	PVP K17
PEG 1000 (M_r = 950–1050)	70% (m/m)
PEG 1500 (M_r = 1400–1600)	70% (m/m)
PEG 2000 (M_r = 1800–2200)	70% (m/m)
PEG 3000 (M_r = 2700–3300)	<5% (m/m)

Investigations after 1 week reveal again a high dissolution rate with high supersaturation for formulations 1–3, whereas formulations 5 and 6 now show in all three batches a slow dissolution without any supersaturation (Fig. 1). The deterioration of the dissolution profile of formulation 5 is shown in Fig. 2 (1 day of storage) and Fig. 3 (1 week of storage), in which the dissolution behaviour of all batches (1–3) is depicted as an area covering the extremes of the three dissolution profiles. This kind of graph has been chosen because the plot of the mean would have suggested a dissolution profile which none of the batches exhibited in fact. The depicted area represents the range in which the dissolution profiles are found. The dissolution characteristics of formulation 6 are very similar to those of formulation 5 (data not shown). Formulation 4 is still inconsistent showing a good dissolution in two batches (Fig. 4).

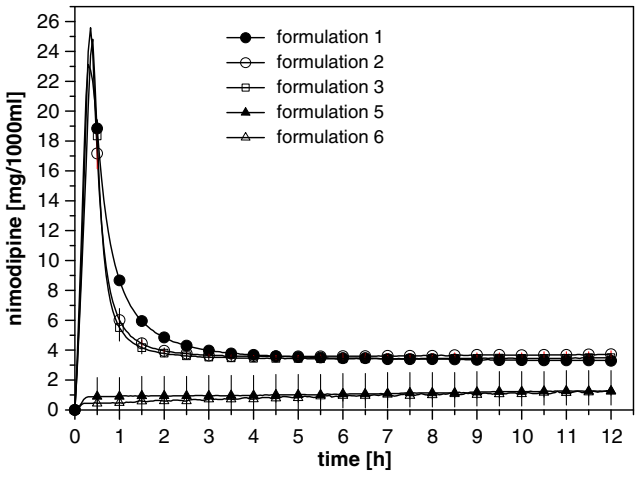

Fig. 1. Dissolution profiles of formulation 1, 2, 3, 5, 6 after 1 week of storage over silica gel at 25 °C, $n = 3$, mean ± extremes.

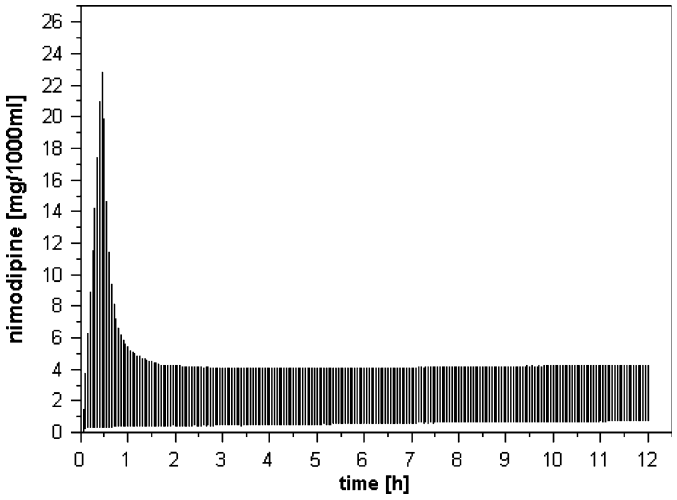

Fig. 2. Dissolution profiles of the three batches of formulation 5 after 1 day of storage over silica gel at 25 °C, $n = 3$, hatched area = range covering the extremes.

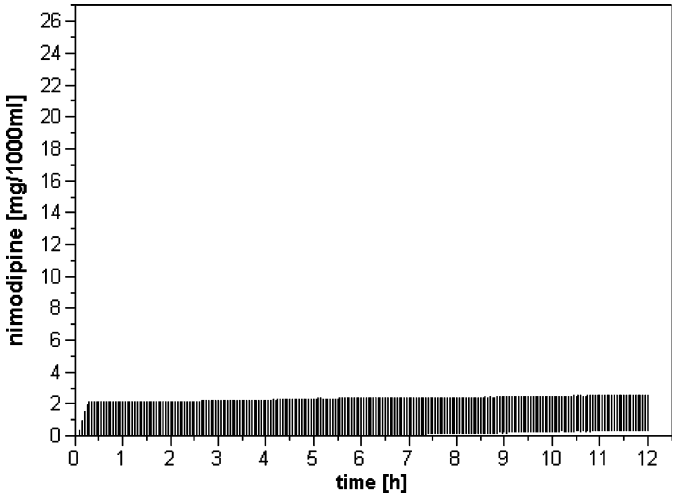

Fig. 3. Dissolution profiles of the three batches of formulation 5 after 1 week of storage over silica gel at 25 °C, $n = 3$, hatched area = range covering the extremes.

After 4 weeks, dissolution profiles are still positive for formulations 1–3 and negative for formulations 5 and 6 (Fig. 5), whereas formulation 4 is admittedly still inconsistent (Fig. 6) but showing a clear degradation in comparison to the dissolution profile after 1 week of storage (Fig. 4).

To investigate the physical status of the drug within the solid dispersions, X-ray diffraction studies have been performed. Diffractograms of pure nimodipine and polyethylene glycol 2000 and 8000 are given for reasons of comparison (Fig. 7), whereas povidone K17 is not depicted. Due of the amorphicity of povidone K17, its diffraction pattern does not show any peaks. Diffractograms of formulations 1, 2, 3, 5 and 6 after 1 week (Fig. 8) as well as after 4 weeks (Fig. 9) of storage at 25 °C over silica gel clearly indicate the absence of crystalline nimodipine in formulations 1, 2 and 3, whereas diffraction peaks of crystalline

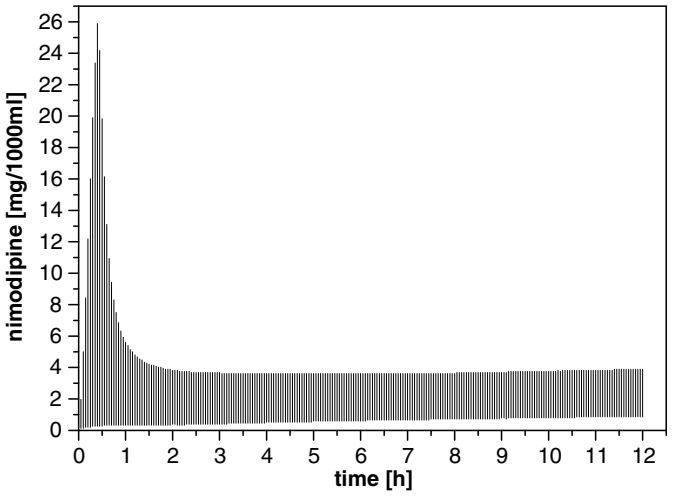

Fig. 4. Dissolution profiles of the three batches of formulation 4 after 1 week of storage over silica gel at 25 °C, $n = 3$, hatched area = range covering the extremes.

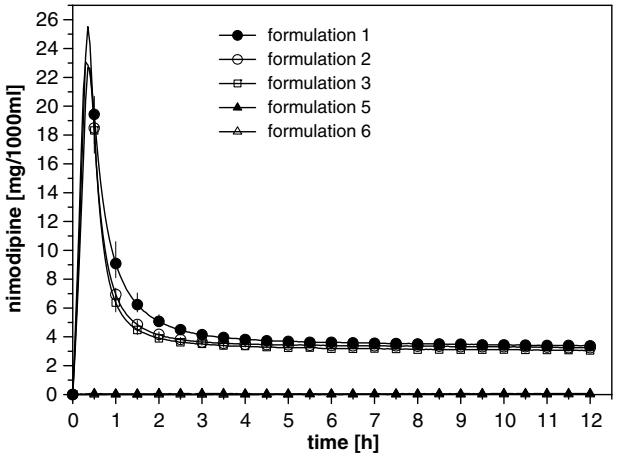

Fig. 5. Dissolution profiles of formulation 1, 2, 3, 5, 6 after 4 weeks of storage over silica gel at 25 °C, $n = 3$, mean ± extremes.

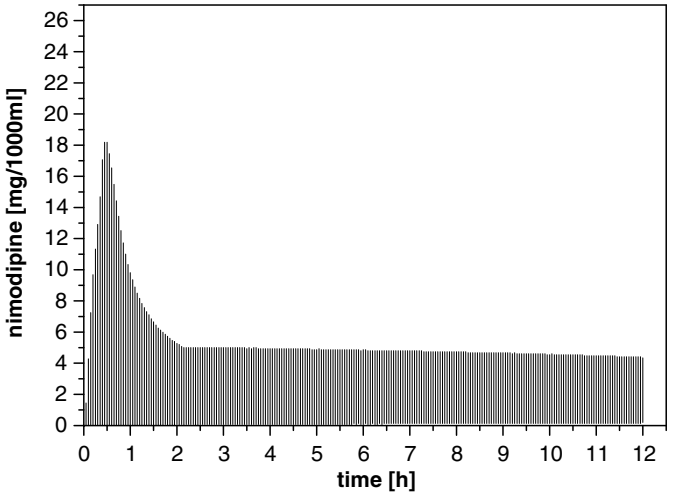

Fig. 6. Dissolution profiles of the three batches of formulation 4 after 4 weeks of storage over silica gel at 25 °C, $n = 3$, hatched area = range covering the extremes.

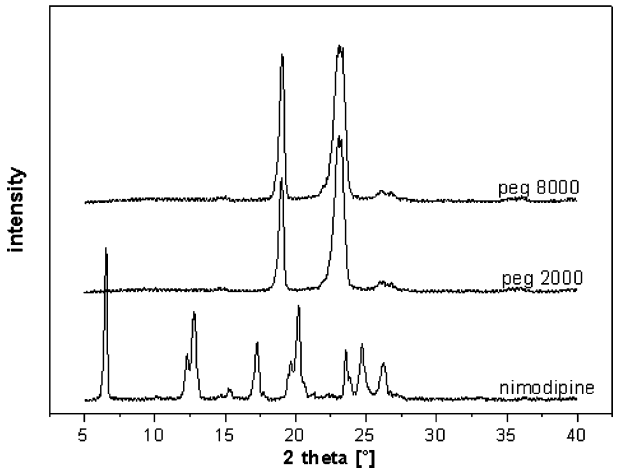

Fig. 7. X-ray diffractograms of powders of pure nimodipine, polyethylene glycol 2000 and polyethylene glycol 8000.

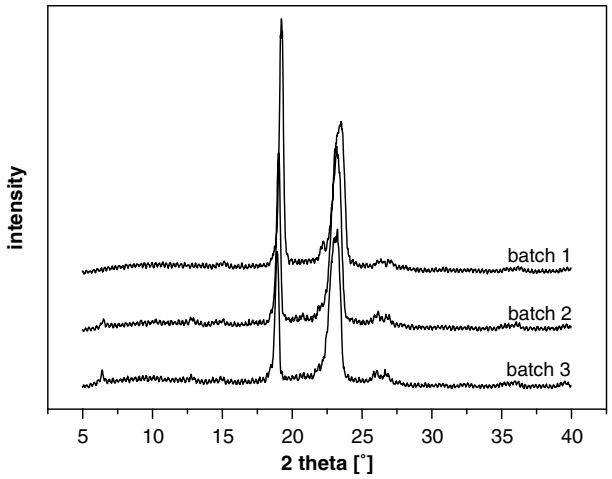

Fig. 10. X-ray diffractograms of different batches of formulation 4 after 1 week of storage over silica gel at 25 °C.

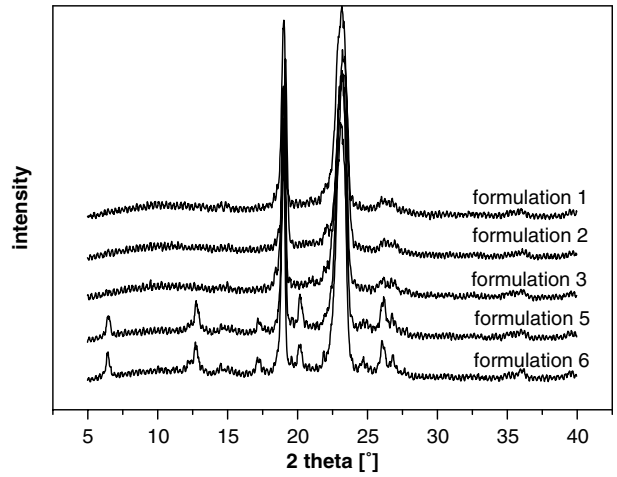

Fig. 8. X-ray diffractograms of formulation 1, 2, 3, 5 and 6 after 1 week of storage over silica gel at 25 °C.

nimodipine in formulations 5 and 6 are present. Fig. 11 shows all three batches of formulation 4 after 4 weeks storage. Compared with 1 week storage (Fig. 10), all three batches show increasing crystallinity. These results support the conclusions drawn from dissolution studies that an adequate inhibition of recrystallization cannot be achieved in formulations 4, 5 and 6 in contrast to formulations 1, 2 and 3.

Investigations by thermal analysis do not confirm these conclusions at first sight. DSC traces of formulations 1 and 6 representing the two extremes in terms of storage stability are described in Figs. 12 and 13.

Thermograms of pure nimodipine, polyethylene glycol 2000 and polyethylene glycol 8000 are given as references (Fig. 14). In none of the DSC traces recrystallization of nimodipine can be proved. This applies for all examined samples. These results are not surprising because of previous studies showing that recrystallization in solid dispersions containing 20% (m/m) nimodipine cannot be

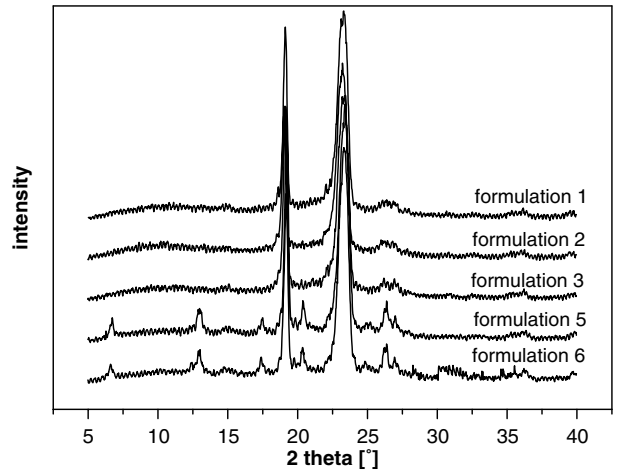

Fig. 9. X-ray diffractograms of formulation 1, 2, 3, 5 and 6 after 4 weeks of storage over silica gel at 25 °C.

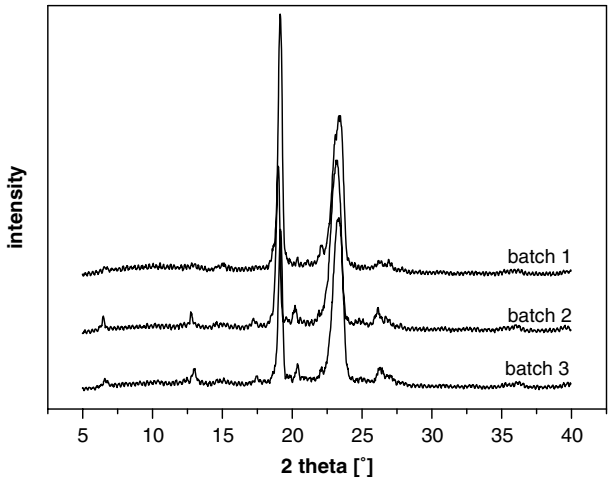

Fig. 11. X-ray diffractograms of different batches of formulation 4 after 4 weeks of storage over silica gel at 25 °C.

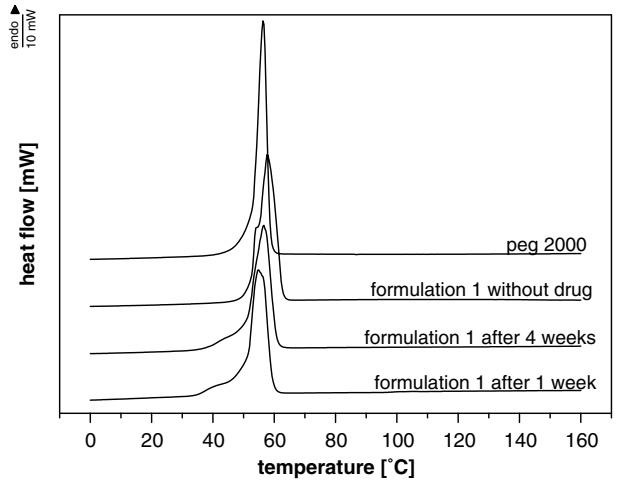

Fig. 12. DSC traces of formulation 1 after 1 week and after 4 weeks, DSC traces of formulation 1 without drug substance and of pure polyethylene glycol 2000 are given as references.

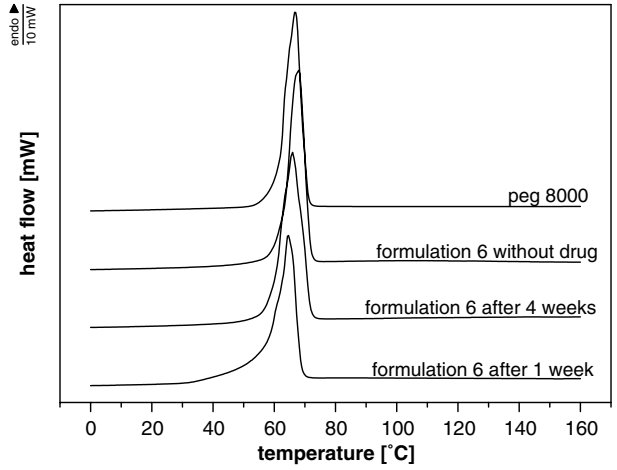

Fig. 13. DSC traces of formulation 6 after 1 week and after 4 weeks, DSC traces of formulation 6 without drug substance and of pure polyethylene glycol 8000 are given as references.

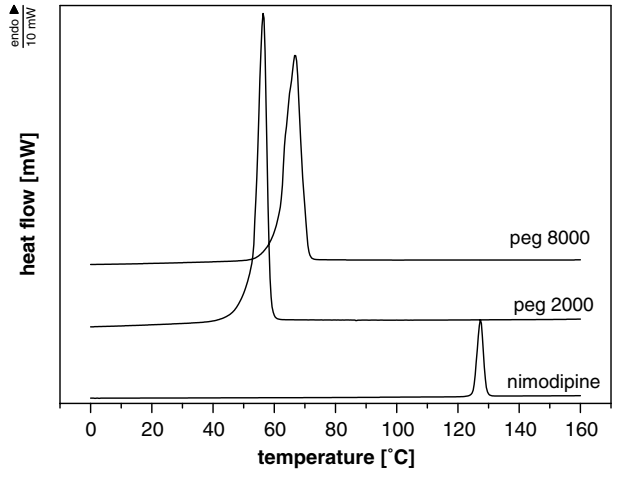

Fig. 14. DSC traces of pure nimodipine, polyethylene glycol 2000 and polyethylene glycol 8000 for references.

detected reliably by differential scanning calorimetry [5]. The reason for this phenomenon becomes clear looking at the phase transitions occurring during the DSC experiment according to the temperature program. The carrier melts at about 50–60 °C, first. Then, recrystallized drug dissolves in the melted carrier successively. As this process covers a comparingly long temperature range and as the enthalpy of this dissolution process is low in comparison to the melting process, generally, the peak connected with this phase transition is broad and not very high. Therefore, the peak might not be significant. This is especially true when bearing in mind, that the amount of drug present in the solid dispersions is only 20%. Furthermore, the endothermic peak caused by the dissolution of the drug in the melted carrier may be partially hidden under the peak caused by the melting carrier as the dissolution of the drug begins immediately after the melting of the carrier. Fig. 12 depicts thermograms of formulation 1 after 1 week and after 4 weeks. DSC traces of formulation 1 without drug and pure polyethylene glycol 2000 are also depicted for comparison. Compared to polyethylene glycol 2000 and the drug-free formulation, the traces of formulation 1 exhibit an additional small hump after 1 and 4 weeks of storage. A change in the ratio of extended and folded chains in favour of folded chains in polyethylene glycol 2000 because of dissolved nimodipine hindering the crystallization of polyethylene glycol 2000 might be a reasonable explanation. High amounts of dissolved molecules always are prone to disturb the formation of the host's crystal lattice, in this special case resulting in a higher amount of folded chains representing the thermodynamically less stable state of polyethylene glycols in comparison to the extended chains [9–17].

In contrast to that, the peak of formulation 6 after 4 weeks of storage does not differ that much from pure polyethylene glycol 8000 and the drug-free formulation. This indicates that the ratio of extended and folded chains in polyethylene glycol 8000 does not change in such extent because of less dissolved nimodipine disturbing the formation of the polyethylene glycol's crystal lattice. By comparing formulation 6 after 1 week and after 4 weeks it is noticeable that the above-mentioned hump has decreased after 4 weeks. An explanation could be the even higher extent of recrystallized nimodipine after 4 weeks so that there is less dissolved nimodipine disturbing the crystal lattice of polyethylene glycol 8000.

Investigations by hot-stage microscopy were also not able to detect recrystallized nimodipine.

Macroscopic observations support the results given by dissolution testing and X-ray diffraction studies. A light yellow, transparent appearance means that recrystallization has not taken place in the sample whereas opaque areas have been shown to indicate recrystallized nimodipine in previous studies [5]. The appearance of opaque areas is caused by the emergence of a second phase, namely the recrystallized nimodipine. As the refractive indices of two phases are usually not equal, the system will be of an

opaque appearance. Formulations 1, 2 and 3 are light yellow and transparent during the whole observation period, formulation 4 partly shows some little opaque dots after 1 week increasing after 4 weeks. Both, formulations 5 and 6 show opaque areas after 1 week, after 4 weeks all samples are completely opaque.

Summarizing the results of the different investigation methods it is clear that recrystallization cannot be inhibited effectively in formulations 4, 5 and 6 whereas in formulations 1, 2 and 3 very probably. Because of the decreasing portion of povidone K17 dissolved in melted polyethylene glycol from formulation 1 (completely dissolved) to formulation 6 (approximately nothing dissolved) there seems to be a correlation between the extent of dissolved povidone K17 and an adequate inhibition of recrystallization and thus, finally, stability. It is still unknown how much povidone K17 needs to be dissolved in the melted polyethylene glycol to prevent the drug from recrystallization, the results of this study permit only a rough estimation.

Future studies will be concerned with the task to get more information about the amount of povidone K17 needed to be dissolved in melted polyethylene glycol in order to guarantee satisfactory storage stability throughout the shelf life of the product.

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