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Research paper

Solid dispersions of nimodipine and polyethylene glycol 2000: dissolution properties and physico-chemical characterisation

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Abstract

The incorporation of a drug in a carrier by melt embedding may either result in a solid solution or in a solid suspension of the active ingredient within the carrier material. As the dispersivity of the drug is of outstanding importance for its dissolution characteristics, parameters which are supposed to influence crystallinity and dispersivity, e.g. cooling rate during preparation and storage conditions like temperature and relative humidity are investigated. It is found that the absence of crystalline drug material in solid dispersions containing nimodipine and polyethylene glycol 2000 is the prerequisite for a high dissolution rate and a remarkable supersaturation in the dissolution medium. Shock freezing during the preparation process, low storage temperatures and low relative humidities are identified to prevent recrystallisation. Furthermore, emphasis is put on the physico-chemical characterisation of solid dispersions. It is shown that the determination of crystallinity and dispersivity of the drug in solid dispersions can only be successful by combining different investigation methods like differential scanning calorimetry, hot stage microscopy, X-ray diffraction as well as macroscopic observation.

Keywords: Dissolution; Nimodipine; Polyethylene glycol; Recrystallisation; Relative humidity; Solid dispersions; Supersaturation; Stability; Storage; Temperature

1. Introduction

The poor solubility of drug substances in water and their low dissolution rate in the aqueous gastro-intestinal fluids often lead to insufficient bioavailability. If the dissolution rate of the active ingredient in the gastro-intestinal liquid is the rate limiting factor for the absorption of the drug, the objective of the formulation will have to be an increase in the dissolution rate. According to the equation of Noyes and Whitney, this may be achieved by an increase in the surface area of the drug which is accessible for the dissolution medium and an enhancement of its solubility.

Beside enhancement of wettability or micronisation of drug substances in order to increase the surface area, and replacement of crystalline drugs by amorphous material in order to increase the solubility, the application of solid dispersions is a method to affect both, surface area and solubility.

A solid dispersion is 'the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or melting-solvent method' [1].

The dispersivity of the drug in the carrier ranges beginning from a suspension of coarse drug particles to a suspension of fine drug particles and finally to a solution of the drug within the carrier, where single drug molecules are dispersed in the carrier material. As particle size decreases in the order mentioned above, the drug surface area which is accessible for the dissolution medium increases in the same order. Furthermore, the solubility of the drug in the dissolution medium is influenced by the interaction of one drug molecule with the surrounding molecules. If the drug molecule forms a crystal lattice with its neighbouring molecules, the solubility will certainly be lower than in an amorphous surrounding. In the case of a solid solution,

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where a drug molecule is surrounded by carrier molecules, the interaction forces between the two will be decisive for the solubility of the drug [2].

In order to receive solid dispersions with the desired dissolution properties, the carrier material has to fulfil certain criteria which favour the dissolution of the solid dispersion in aqueous media like high wettability by and solubility in water.

Furthermore, the manufacturing process is of remarkable importance for the dissolution characteristics of solid dispersions because of the influence on dispersivity and molecular arrangement of drug and carrier. In general, the active substance may be incorporated in the carrier material by coevaporation, where a solution of both components in a common organic solvent is evaporated, by melt embedding or a combination of both [1,3,4]. In contrast to the coevaporation method, the melting procedure seems to be more convenient because of the simple manufacturing process and the lack of solvent removal and recovery, which ensures a cost-effective method of production. Nevertheless, the thermal stress connected with this preparation mode means a certain drawback [1,4,5]. Polyethylene glycol is commonly known as a typical carrier material for melt embeddings. Due to its low melting point and high ability to dissolve many drug substances in the melted state, the thermal stress for the drug usually stays low [6].

However, for the majority of solid dispersion preparations, polyethylene glycols with molecular weights ranging from 4000 to 20,000 were used [11], especially polyethylene glycol 4000 and 6000 [6]. As it is known from the literature, polyethylene glycol 4000 and 6000 may crystallise as extended and once folded chains, the latter being metastable with respect to extended chains [7–15]. Therefore, the conversion of the metastable once folded form to the extended form is likely upon storage [16]. Furthermore, a rapid cooling process during preparation of solid dispersions by the melting method may provoke the formation of the metastable once folded form, whereas slow cooling may lead to extended polymer chains. This may complicate the characterisation of solid dispersions [11]. Additionally, the highest degree of crystallinity has been reported for polyethylene glycol 6000 [13] which limits the formation of molecular dispersions of the drug within this carrier material. Low molecular weight polyethylene glycols, on the contrary, have not been intensively studied as solid dispersion carrier materials in the past. Beside the fact, that lower molecular weight polyethylene glycols crystallise only in the extended form ($M_r < 3000$) [9,10], they exhibit several further advantages. Usually, the solubility of drugs within polyethylene glycols increases with decreasing molecular weight [17] thereby favouring the formation of solid solutions. Furthermore, the viscosity decreases with decreasing molecular weight [17] providing the prerequisite for a fast dissolution rate of dispersion which dissolve carrier-controlled [11]. On the contrary, the lower viscosity of low molecular weight polyethylene glycols means a certain drawback regarding their potency to prevent the drug from recrystallising during the cooling process of solid dispersions prepared by the fusion method and during storage. Furthermore, precipitation of the drug within the dissolution medium will be prevented more effectively by highly viscous polyethylene glycols [6]. Another disadvantage is the increasing hygroscopy with decreasing molecular weight [6,17]. Both, high hygroscopy and low crystallisation inhibition may lead to changes of solid dispersion systems upon ageing. Therefore, storage stability has to be carefully investigated. Nevertheless, in this study polyethylene glycol 2000 was chosen as carrier material to investigate whether the advantages of low molecular weight polyethylene glycols result in solid dispersions with favourable dissolution profiles containing the calcium channel blocking agent nimodipine. Although solid dispersions containing nifedipine and polyethylene glycols, especially polyethylene glycol 4000 [18–22] and 6000 [18–21,23,24] have been extensively studied in the literature, partially with contradictory results regarding the proposed crystalline state of the drug, little has been published about nimodipine [25,26].

Considering all these factors, it has to be borne in mind that solid suspensions containing metastable crystalline or amorphous drug material as well as supersaturated solid solutions represent thermodynamically unstable systems which tend to convert into a more stable state during preparation and storage [19,20,27–32]. Thus, careful investigation of the physico-chemical nature of solid dispersions is essential for an understanding of changes within these systems during preparation and storage. These experiments form the prerequisite for an efficient development of solid dispersions with rapid dissolution and good storage stability.

Therefore, the following investigations focus on the influence of the mode of preparation and storage on the dissolution quality of solid dispersions. Furthermore, a powerful instrument consisting of methods belonging to thermal analysis, X-ray diffraction and simple macroscopic observation will be proposed which allows a reliable characterisation of the physico-chemical status of solid dispersions containing nimodipine and polyethylene glycol 2000.

2. Materials and methods

2.1. Materials

Nimodipine, Ph. Eur., was provided by Bayer AG, D-Leverkusen. *Polyethylene glycol 300* (see Macrogole Ph. Eur.) was given by Clariant GmbH, D-Burgkirchen and *polyethylene glycol 2000* (see Macrogole Ph. Eur.) by Hoechst AG, D-Frankfurt am Main.

2.2. Methods

2.2.1. Preparation and storage of solid dispersions and solid suspensions

Solid dispersions of 20 and 40% drug content were prepared by heating polyethylene glycol 2000 and nimodipine until the drug was dissolved completely in the melt and an homogenous solution was obtained. The necessary temperature is 110 °C for systems containing 20% of nimodipine and 120 °C for dispersions with a drug content of 40%. After dissolution was completed, the solution was brought to solidification by pouring it into tablet moulds, which had a temperature of either +25 or −20 °C. In the first case the arising systems are called slow cooled, in the latter shock cooled or shock frozen solid dispersions. Immediately after the solidification, the dispersions were kept for 24 h over silica gel at +25 or −20 °C, respectively. After this storage time of 24 h, shock frozen samples were further stored either at −20 °C over silica gel, or at +25 °C over silica gel, as well as at 60% rh. Slow cooled solid dispersions were kept at +25 °C over silica gel, as well as 60% rh. After an overall storage period of one day, two days or four weeks, solid dispersions were investigated by dissolution testing, thermal analysis, X-ray diffraction and macroscopic observation. Additional macroscopic investigations were performed after three and four days of storage. Table 1 lists cooling and storage conditions and the corresponding abbreviations (in bold letters) used to mark these conditions in figures and tables.

Solid suspensions of 20 and 40% drug content were prepared by heating polyethylene glycol 2000 until it was completely melted at +65 °C and by suspending nimodipine in the melt. In order to avoid dissolution of nimodipine in polyethylene glycol 2000, the carrier was heated minimally over its melting point, and the process of suspending the drug was kept as short as possible. The suspension was brought to solidification by pouring it into tablet moulds, which had a temperature of +25 °C. Solid suspensions were further kept at +25 °C over silica gel prior to the investigations.

2.2.2. Dissolution studies of solid dispersions and solid suspensions

A paddle apparatus (DT 6 R, ERWEKA, D-Heusenstamm) according to Ph. Eur. 2002 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 three minutes. The nimodipine concentration was determined spectrophotometrically in flow-through cells (Lambda-2-Spectrometer, Perkin Elmer, D-Überlingen) at $\lambda = 238$ 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).

2.2.3. Differential scanning calorimetry (DSC)

Thermal investigations were performed using a DSC 30 (Mettler-Toledo AG, D-Gießen). The temperature ranged from 0 to 170 °C with a heating rate of 10 °C/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 (5 mg) of the tablets prepared as described in Section 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.

2.2.4. 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 Section 2.2.1 using a razor blade.

2.2.5. 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 used for X-ray analysis, which had a temperature of either +25 or −20 °C.

2.2.6. Macroscopic observation

Photographs of solid dispersions were taken using a Minolta SRT 303 b (Minolta, J-Osaka). Sample preparation was done by pouring the melt directly into Petri-dishes with a diameter of 3 cm, which had a temperature of either +25 or −20 °C.

2.2.7. Solubility of nimodipine in polyethylene glycol 300 at +25 and +65 °C

The solubility of nimodipine in polyethylene glycol 300 was determined visually by adding 1–10% of nimodipine to the liquid polyethylene glycol 300 in 1% steps and stirring it in small vessels at +25 and +65 °C for five days.

2.2.8. Solubility of nimodipine in polyethylene glycol 2000 at +65 °C

The solubility of nimodipine in polyethylene glycol 2000 was determined by adding 20–25% of nimodipine to polyethylene glycol 2000 in 1% steps and heating the mixture up to +65 °C. After five days of stirring at +65 °C in small vessels, the solubility of nimodipine in liquid polyethylene glycol 2000 was determined visually.

2.2.9. Sieve analysis of nimodipine

The particle size distribution was determined by sieve analysis using a sieving machine (AS 200 control, Retsch

Table 1
Abbreviations of preparation and storage conditions as well as of the time of investigation (in bold letters) for solid dispersions

cooling down to -20°C ↓ storage at -20°C / silica gel			cooling down to +25°C ↓ storage at +25°C / silica gel	
first investigation after one day (**1d**) of storage				
20 / 1d			**25 / 1d**	
↙ storage at -20°C / silica gel	↓ storage at +25°C / silica gel	↘ storage at +25°C / 60% rh	↙ storage at +25°C / silica gel	↘ storage at +25°C / 60% rh
second investigation after two days (**2d**) of storage				
20 / 20,00 / 2d	**20 / 25,00 / 2d**	**20 / 25,60 / 2d**		
↓ storage at -20°C / silica gel	↓ storage at +25°C / silica gel	↓ storage at +25°C / 60% rh		
third investigation after three days (**3d**) of storage				
20 / 20,00 / 3d	**20 / 25,00 / 3d**	**20 / 25,60 / 3d**		
↓ storage at -20°C / silica gel	↓ storage at +25°C / silica gel	↓ storage at +25°C / 60% rh		
fourth investigation after four days (**4d**) of storage				
20 / 20,00 / 4d	**20 / 25,00 / 4d**	**20 / 25,60 / 4d**		
↓ storage at -20°C / silica gel	↓ storage at +25°C / silica gel	↓ storage at +25°C / 60% rh		
fifth investigation after four weeks (**4w**) of storage				
20 / 25,00 / 4w	**20 / 25,60 / 4w**	**20 / 25,60 / 4d**		

GmbH & Co. KG, D-Haan). Samples were sieved for 20 min at a vibration height of 1.5 mm. Sieves diameters were 200 mm, sieve meshes were 45, 63, 100, 140, 180, 200, 315, 400 and 715 μm.

3. Results and discussion

3.1. Influence of the mode of preparation

Solid dispersions were prepared by the melting method. Nimodipine and polyethylene glycol 2000 were heated until the dissolution of the drug within the carrier was complete. Subsequently, the solution was cooled down.

As the solubility of most chemical entities decreases with decreasing temperatures, the liquid solution of the drug in the melted carrier probably turns into a saturated and, with further cooling, into a supersaturated solution. At this point, the solubility of the drug will be exceeded and the solution will turn into a suspension, if the molecular mobility in the liquid is sufficiently high and the cooling progress sufficiently slow to allow the drug to recrystallise. As the cooling rate increases, the time for the transition of the liquid solution into the solid state and for the recrystallisation process

decreases, thereby favouring the creation of thermodynamically unstable supersaturated solid solutions. Therefore, the cooling mode seems to be crucial for the physico-chemical properties of solid dispersions [6,18,33–35].

Unfortunately, solubilities of substances in solid phases are difficult to determine. In order to get a rough idea of the magnitude of the solubility of nimodipine in polyethylene glycol 2000, first, the solubility of nimodipine in polyethylene glycol 300, which is liquid was determined. Breitenbach et al. [36] described this type of comparison for the estimation of the solubility of drugs in polyvinylpyrrolidone by liquid vinylpyrrolidone. Regarding polyethylene glycols, it is described that the solubility of substances increases with increasing temperatures, but decreases with increasing molecular weight of the polyethylene glycol [17]. In this study, the solubility of nimodipine in polyethylene glycol 300 was examined at +25 and +65 °C. As polyethylene glycol 2000 is a solid at +25 °C, the solubility of nimodipine was determined in melted polyethylene glycol 2000 at +65 °C. The solubility of nimodipine in polyethylene glycol 300 is found to be 5% at +25 °C and 20% at +65 °C. The solubility of nimodipine in liquid polyethylene glycol 2000 at +65 °C is 22% which is slightly higher than in polyethylene glycol 300 and therefore, in this point does not conform exactly to the above mentioned reference. Transferring the results from +65 to +25 °C, the solubility of nimodipine in crystalline polyethylene glycol 2000 at +25 °C should be around 5% or even lower, because the solubility of a substance in a crystalline solid is usually lower than in a liquid. This means, that solid dispersions containing 20 or 40% nimodipine are supersaturated regarding the drug, and the risk for recrystallisation taking place during the cooling process becomes evident. Therefore, the two different cooling modes may affect the crystallinity and dispersivity of the drug in solid dispersions of nimodipine and polyethylene glycol 2000.

The dissolution characteristics of slow cooled and shock frozen solid dispersions containing 20 and 40% of nimodipine in polyethylene glycol 24 h after preparation are shown in Figs. 1 and 2, respectively. Slow cooled systems were stored at +25 °C over silica gel prior to the investigations, whereas the shock frozen systems were kept at −20 °C over silica gel.

Shock frozen solid dispersions containing 20% nimodipine show a very high dissolution rate and an about threefold supersaturation of the drug in the dissolution medium compared to the solubility of nimodipine. In contrast, slow cooled solid dispersions exhibit a lower dissolution rate without any supersaturation effects. However, the dissolution is slightly faster compared to the reference, which is a solid suspension of nimodipine in polyethylene glycol 2000, obtained by melting the carrier and dispersing, but not dissolving the drug within the liquid carrier material.

The dissolution rate of shock frozen solid dispersions containing 40% nimodipine is superior with regard to slow cooled systems, but both systems lack pronounced supersaturation effects ($c_{s\ (37\ °C)}$ = 3.3 mg/l). The dissolution rate of the corresponding solid suspension is hardly lower in comparison to slow cooled solid dispersions.

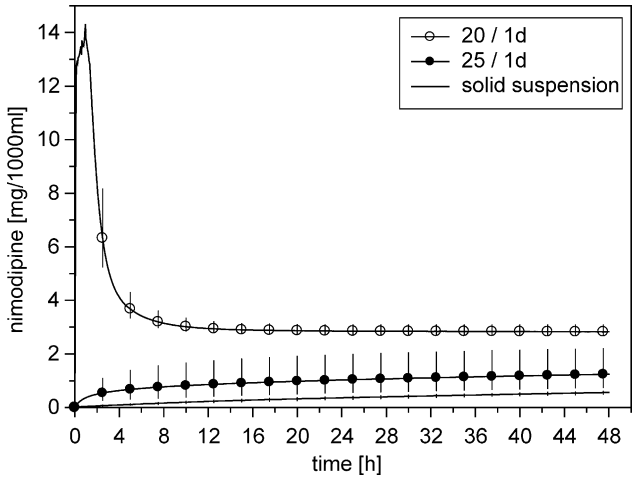

Fig. 1. Dissolution profiles of shock frozen and slow cooled solid dispersions containing 20% of nimodipine after 24 h of storage over silica gel at −20 and +25 °C; abbreviations see Table 1; dissolution profile of solid suspension is given as reference; $n = 3 \pm$ range.

In order to find an explanation for the above mentioned differences in the dissolution rates especially for shock frozen and slow cooled solid dispersions containing 20% of drug and in order to get an insight into their physico-chemical properties, investigations were performed using methods of thermal analysis and X-ray diffraction. Fig. 3 depicts DSC traces of shock frozen and slow cooled solid dispersions containing 20 and 40% of nimodipine. The thermograms of the pure carrier powder as well as of the pure drug material are given as references. The DSC trace of pure nimodipine exhibits two endotherms which are ascribed to its two modifications. Nimodipine is a racemate.

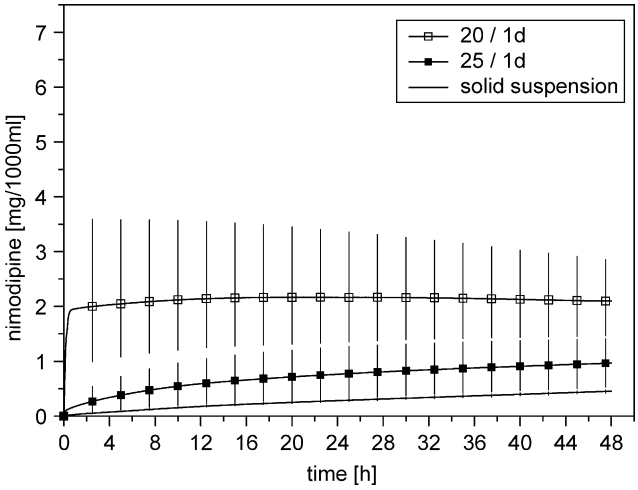

Fig. 2. Dissolution profiles of shock frozen and slow cooled solid dispersions containing 40% of nimodipine after 24 h of storage over silica gel at −20 and +25 °C; abbreviations see Table 1; dissolution profile of solid suspension is given as reference; $n = 3 \pm$ range.

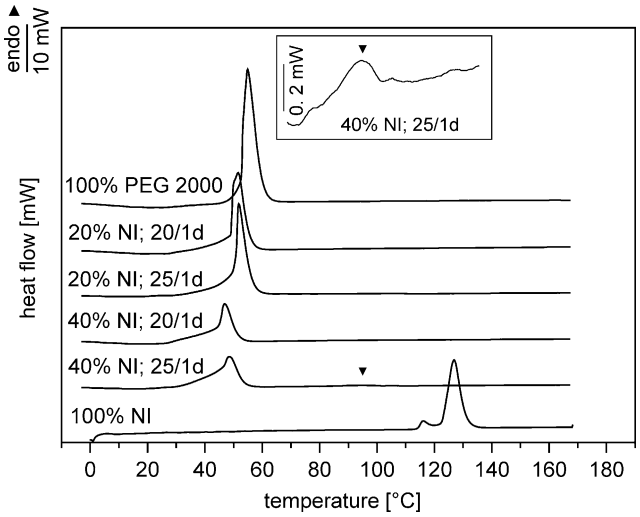

Fig. 3. DSC traces of shock frozen and slow cooled solid dispersions containing 20% of nimodipine (20% NI) and 40% of nimodipine (40% NI) after 24 h of storage over silica gel at −20 and +25 °C; abbreviations see Table 1; DSC traces of 100% nimodipine powder (100% NI) and 100% polyethylene glycol 2000 (100% PEG 2000) powder are given as references; the first of two measurements is shown.

According to Grunenberg et al. [37] it crystallises in two modifications. Modification I melts at 124 °C and modification II at 116 °C. Modification II is a conglomerate of the two pure enantiomers, whereas modification I represents a racemic compound. However, the mixture of the two modifications usually shows three endothermic peaks. First, modification II melts at 116 °C. Then, at 122 °C the eutectic mixture consisting of modification I (the racemic compound) and one of the pure enantiomers melts, followed by the melting of modification I at 124 °C [37]. Due to the high scanning rate of 10 K/min the latter two peaks appear as one single endotherm. The investigated solid dispersions exhibit up to two endothermic effects. The first peak represents the melting of polyethylene glycol 2000 between 50 and 60 °C and, where crystalline drug material is present, a second facultative peak stands for the dissolution of nimodipine in the melt. However, this second peak can be observed only in slow cooled solid dispersions containing 40% of nimodipine (marked by an arrow). Obviously, recrystallisation of the drug has taken place during preparation and/or storage due to a supersaturation of the drug within the carrier. However, differences of shock frozen and slow cooled solid dispersions containing 20% of nimodipine cannot be detected by using differential scanning calorimetry.

Table 2 represents the results of experiments performed by hot stage microscopy (HSM). As already has been stated by DSC-experiments, investigations by HSM with polarised light confirm for slow cooled solid dispersions containing 40% of nimodipine, that after the melting of polyethylene glycol 2000 very fine crystals, which remain in the melt, subsequently dissolve with rising temperatures. When investigating shock frozen solid dispersions

Table 2
Observations by HSM of shock frozen and slow cooled solid dispersions containing 20% of nimodipine (20% NI) and 40% of nimodipine (40% NI) after 24 h of storage over silica gel at −20 and +25 °C

	Melting of polyethylene glycol 2000	Remaining crystals of nimodipine	Crystal growth of nimodipine crystals	Dissolution of nimodipine crystals
20% NI; 20/1d	+	−	−	−
20% NI; 25/1d	+	+	−	+
40% NI; 20/1d	+	+	+	+
40% NI; 25/1d	+	+	−	+

For abbreviations see Table 1; (+) detectable, (−) not detectable.

containing 40% of nimodipine, these observations can be made as well, although there is a smaller amount of remaining crystals after the melting of polyethylene glycol 2000. Moreover, these crystals grow until the temperature is high enough to let them dissolve again. This phenomenon of crystal growth may be explained by an incomplete recrystallisation of the drug taking place during preparation and/or storage. Taking into consideration a lower molecular mobility of the drug molecules at −20 °C instead of +25 °C the reason for an incomplete recrystallisation process becomes evident. Unfortunately, the enthalpy changes connected with the described recrystallisation and subsequent dissolution of shock frozen solid dispersions containing 40% of nimodipine are too small to be detected by DSC. This is due to very small amounts of drug undergoing these transitions [27]. Furthermore, especially the dissolution process in comparison to melting processes is connected with small enthalpy changes covering a wide temperature range. Therefore, the related peak is very small and can often not be distinguished from the baseline [38–40].

Like slow cooled systems containing 40% of nimodipine, slow cooled solid dispersions containing 20% of nimodipine first reveal the melting of polyethylene glycol 2000 and, as temperature increases, the dissolution of crystals, which have been remaining in the melt. Again, DSC-experiments fail to detect the enthalpy changes related to this transition. In contrast to slow cooled solid dispersions, only one thermal effect can be observed by HSM on shock frozen solid dispersions containing 20% of nimodipine, namely the melting of polyethylene glycol 2000. After this first melting process the melt appears isotropic and lacks any crystals within. On the one hand, these observations may be explained by a lower molecular mobility of the shock frozen systems in comparison to slow cooled solid dispersions containing 20% of nimodipine. On the other hand, the supersaturation level of solid dispersions containing 20% of nimodipine is less than of those systems containing 40% of the drug. Therefore, the drug does not undergo recrystallisation as long as supersaturation level and molecular mobility are sufficiently low, thereby ensuring a favourable dissolution profile with a fast

dissolution rate and a pronounced supersaturation of the drug in the dissolution medium.

The slightly higher dissolution rates of slow cooled solid dispersions containing 20% nimodipine and of solid dispersions containing 40% nimodipine in comparison to their corresponding solid suspensions may be attributed to the difference of the nimodipine crystal size within the two systems. As described by Craig [11], a drug-controlled dissolution is highly dependent on the properties of the drug like, for example, its particle size. In contrast to carrier-controlled dissolution, where the drug dissolves easily in the adjacent polymer rich layer, drug-controlled dissolution means, that the drug is released as undissolved intact particle and has to dissolve after it has left the adjacent layer in the dissolution medium. The median diameter of the nimodipine powder which was used for the preparation of solid suspensions is 184.5 μm determined by sieve analysis. According to the preparation mode of solid suspensions described in Section 2.2.1, particle size of nimodipine should remain unaffected by the manufacturing process [41]. In contrast, the particle sizes of nimodipine crystals in slow cooled solid dispersions containing 20% nimodipine and of solid dispersions containing 40% nimodipine determined during the HSM investigations (Table 2) is about 10-fold smaller. Unfortunately, it is not possible to determine the particle size distribution exactly, due to the very fast changes which particle sizes are subjected to during the HSM heating process.

Furthermore, the preparation of slow cooled solid dispersions containing 20% nimodipine and of solid dispersions containing 40% nimodipine may have induced changes to the modifications of nimodipine with regard to the corresponding solid suspensions. As this study focuses on the preparation of solid dispersions containing the drug in the amorphous or even molecularly dispersed state, the investigation of polymorphism in the solid dispersions was beyond the scope of this study.

In order to confirm the differences in crystallinity between shock frozen and slow cooled solid dispersions containing 20% of nimodipine, investigations by X-ray diffraction were performed. The diffraction patterns shown in Fig. 4 clearly indicate the presence of crystalline nimodipine (marked by an arrow) in slow cooled systems containing 20% of nimodipine, whereas shock frozen dispersions with a drug amount of 20% lack any peaks which could have been caused by crystalline drug material.

These results clearly demonstrate the influence of the cooling rate on the properties of solid dispersions obtained by the melting method. Regarding solid dispersions containing 20% of the drug, the shock freezing process favours the formation of solid solutions with favourable dissolution properties whereas a low cooling rate provokes recrystallisation of the drug within the carrier leading to solid suspensions with an deteriorated dissolution profile [18]. The same principle can be found when the drug amount is raised to 40%. But, in contrast to systems containing only 20% of drug material, the supersaturation level is too high to suppress recrystallisation processes even in shock frozen systems. Consequently, solid suspensions are obtained and the dissolution properties are comparatively disadvantageous. Nevertheless, recrystallisation in shock frozen systems is somewhat lower and in comparison to slow cooled systems incomplete, which is documented by additional recrystallisation effects detectable by HSM-investigations in shock frozen systems during the heating process, when the molecular mobility becomes high enough to allow the system to recrystallise completely. However, it has to be borne in mind that shock frozen solid dispersions represent thermodynamically unstable systems that risk to convert into a thermodynamically stable state.

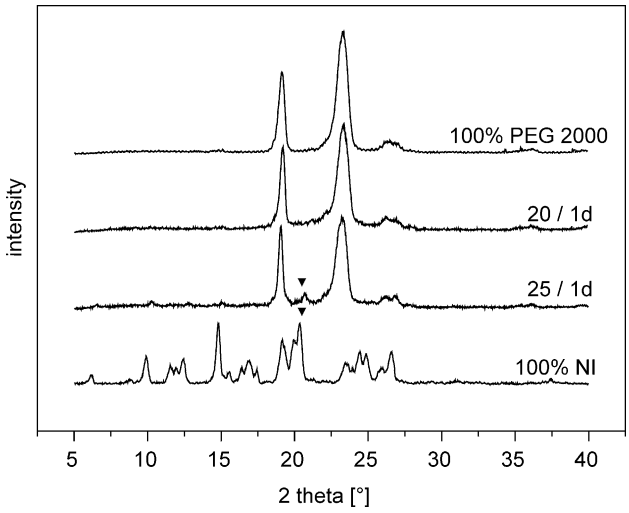

Fig. 4. X-ray diffractograms of shock frozen and slow cooled solid dispersions containing 20% of nimodipine after 24 h of storage over silica gel at −20 and +25 °C; abbreviations see Table 1; the first of two measurements is shown. Pure polyethylene glycol 2000 and pure nimodipine are shown as references.

3.2. Influence of storage conditions

As shock frozen solid dispersions have been found being thermodynamically unstable systems and temperature has turned out to be an important factor regarding molecular mobility, the following part will be concerned with the investigation of the influence of storage conditions, namely storage temperature and relative humidity. Therefore, the changes in the dissolution properties of shock frozen solid dispersions containing 20% of nimodipine caused by different storage conditions were investigated.

3.2.1. Influence of temperature

In order to evaluate the influence of the storage temperature on the dissolution properties, solid dispersions containing 20% of nimodipine were prepared by shock freezing. After a primary storage period of 24 h at −20 °C, the systems were stored for four weeks either at −20 °C or at +25 °C over silica gel prior to the investigations. Fig. 5

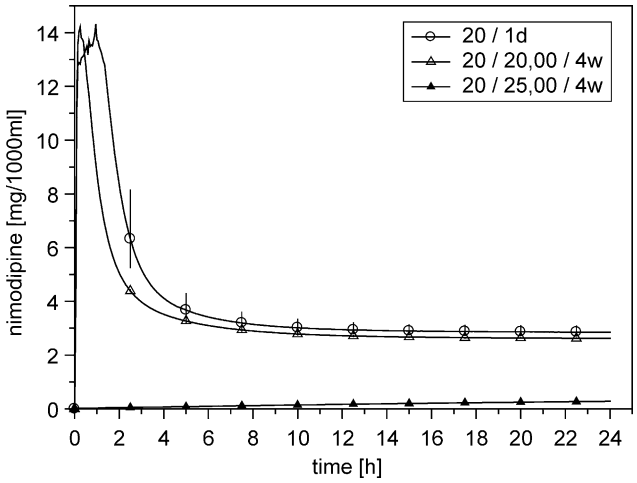

Fig. 5. Dissolution profiles of shock frozen solid dispersions containing 20% of nimodipine after 4 weeks of storage at −20 and +25 °C over silica gel; abbreviations see Table 1; dissolution profile of shock frozen solid dispersions containing 20% of nimodipine after 24 h of storage over silica gel at −20 °C is given as reference; $n=3\pm$range.

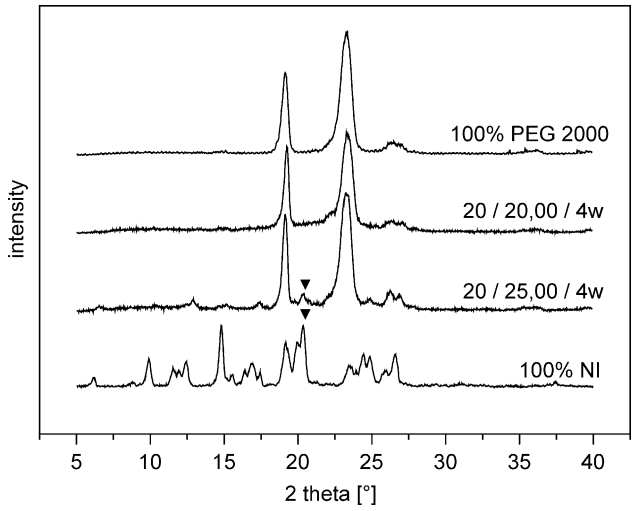

Fig. 6. X-ray diffractograms of shock frozen solid dispersions containing 20% of nimodipine after 4 weeks of storage at −20 and +25 °C over silica gel; abbreviations see Table 1; the first of two measurements is shown. Pure polyethylene glycol 2000 and pure nimodipine are shown as references.

depicts the corresponding dissolution characteristics. The dissolution profile of shock frozen solid dispersions after 24 h storage at −20 °C is given as reference. In comparison to shock frozen systems after 24 h of storage at −20 °C, solid dispersions which were stored at −20 °C over silica gel for four weeks exhibit nearly the same dissolution properties characterised by a fast dissolution rate and a high supersaturation level in the dissolution medium. Only the time frame in which the supersaturation level is maintained is of a slightly shorter duration. In contrast, shock frozen solid dispersions that were stored at +25 °C over silica gel for 4 weeks exhibit a slow dissolution rate and lack any supersaturation effects. It may be supposed, that, due to a higher storage temperature, molecular mobility raises, thereby favouring recrystallisation phenomena [42,43].

This suggestion has been proven by X-ray diffraction. Fig. 6 clearly indicates the presence of drug crystals in solid dispersions stored at +25 °C, whereas peaks of nimodipine cannot be detected in systems kept at −20 °C.

3.2.2. Influence of relative humidity

To get an insight into changes caused by different relative humidities, shock frozen solid dispersions containing 20% of nimodipine were stored at +25 °C either over silica gel or at 60% rh after the first storage period of 24 h at −20 °C. After a storage time of four weeks, the dissolution characteristics were evaluated. Fig. 7 shows, that hardly any differences in the dissolution profiles can be detected between the two. Both profiles are characterised by a slow dissolution rate and the absence of supersaturation effects. From these data it may be derived on the one hand, that the dissolution properties are not affected by different relative humidities. On the other hand increasing relative humidities should promote recrystallisation by favouring the uptake of water thereby enhancing molecular mobility [44]. This has been described in many studies investigating the storage stability of solid dispersions [20,30–32,44–48]. Moreover, penetrating water deteriorates the capacity of the carrier material to dissolve the poorly water soluble drug thereby favouring recrystallisation as well. A possible explanation for this contradiction may be the following. Since thermodynamically unstable systems always tend to convert into the thermodynamically stable state, shock frozen systems which have been identified to be supersaturated solutions are subjected to changes. These transitions will take a certain time to be completed, but if the system reaches the thermodynamically stable state, it will stay at this endpoint without changing anymore. In order to find out whether both systems have already reached this state, the same experiment was repeated, but investigations were performed after only two days of storage.

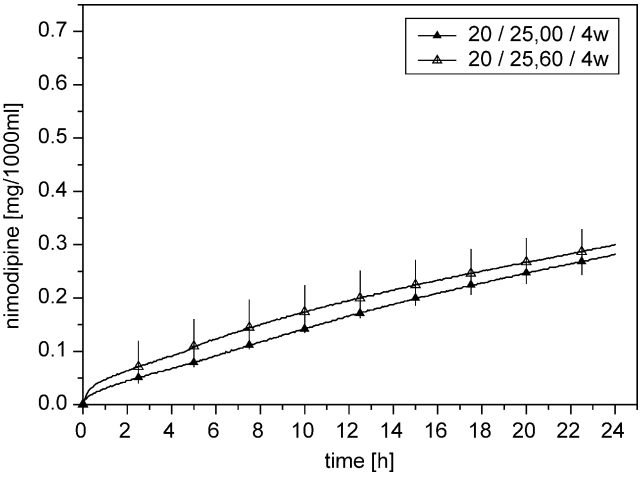

Fig. 7. Dissolution profiles of shock frozen solid dispersions containing 20% of nimodipine after 4 weeks of storage at +25 °C over silica gel and at 60% rh; abbreviations see Table 1; $n=3\pm$range.

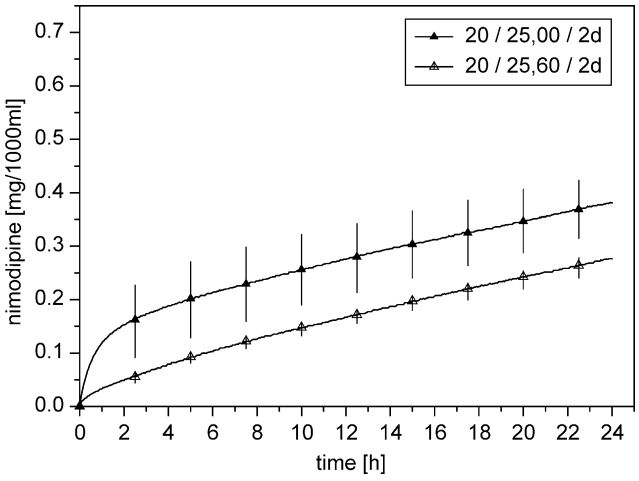

Fig. 8. Dissolution profiles of shock frozen solid dispersions containing 20% of nimodipine after 2 days of storage at +25 °C over silica gel and at 60% rh; abbreviations see Table 1; $n=3\pm$range.

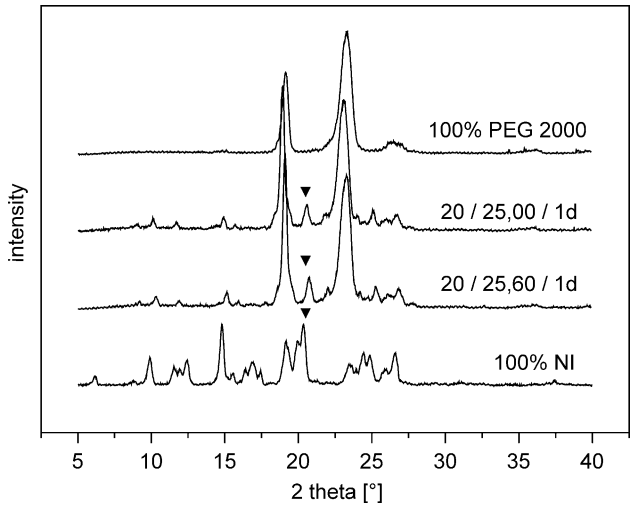

Fig. 9. X-ray diffractograms of shock frozen solid dispersions containing 20% of nimodipine after 2 days of storage at +25 °C over silica gel and at 60% rh; abbreviations see Table 1; the first of two measurements is shown. Pure polyethylene glycol 2000 and pure nimodipine are shown as references.

In contrast to investigations carried out after four weeks of storage, dissolution testing after a storage period of two days detects a difference between systems that were stored over silica gel or at 60% rh (Fig. 8). Although both samples do not show any supersaturation effects anymore, systems which were kept over silica gel exhibit a slightly faster dissolution rate compared to solid dispersions stored at 60% rh. Since supersaturation phenomena cannot be observed, it is very probable that recrystallisation has occurred in both systems already, but the extent of recrystallisation is expected to be different causing the described differences of the dissolution rate.

In order to prove this assumption, investigations were carried out using thermal analysis, X-ray diffraction as well as macroscopic observations.

Unfortunately, a difference cannot be detected between the two samples by DSC (data not shown). Both traces exhibit only one thermal transition representing the melting of polyethylene glycol 2000. Additional investigations by HSM reveal, that after the melting of polyethylene glycol 2000 some crystals remain in the melt which subsequently dissolve with raising temperatures. This effect is also stated in both systems and a differentiation between the two regarding the amount of remaining crystals is difficult due to the more qualitative nature of microscopic observations.

Investigations by X-ray diffraction either do not contribute to clarify the physico-chemical differences (Fig. 9). Both patterns exhibit diffraction peaks of crystalline nimodipine, but a quantification of the amount of recrystallised material is difficult, because not only the amount but also the size and orientation of the embedded crystals define the area under the diffraction peak, which is indicative for the amount of recrystallised material. As the size of recrystallised particles in solid dispersions and the orientation of the same cannot be controlled or standardised by sample preparation, unless the sample is ground, which on the other hand means a certain stress to the sample and a risk to introduce artefacts into the system, the determination of recrystallised material stays difficult.

Simple macroscopic observations were carried out (Fig. 10), in search of an examination method explaining the differences between the dissolution profiles of shock frozen solid dispersions which were stored at +25 °C either over silica gel or at 60% rh. Shock frozen solid dispersions which were stored for 24 h at −20 °C over silica gel are of a light yellow, transparent appearance. After storage periods of two, three or four days at −20 °C, the initial state is maintained, whereas solid dispersions change into a predominantly transparent material but with small opaque dots in it, when the shock frozen systems are stored at +25 °C over silica gel. Storage at +25 °C and 60% rh leads to even bigger opaque areas. The difference between the two systems becomes even more evident after a storage period of three or four days (Fig. 10). The emergence and growing of opaque dots within the initially transparent appearing system is synonymous with the development of crystal seeds and crystal growth of the drug, briefly with the development of a second crystalline phase within the initially homogenous system. Due to different refractive indices of the two phases, the resulting system appears heterogenous. In order to provide direct evidence that the opaque areas represent areas where nimodipine is in the crystalline state whereas transparent areas do not contain recrystallised drug material, investigations were performed by X-ray diffraction of completely transparent and of completely opaque areas (Fig. 11). The X-ray diffraction patterns of slow cooled solid dispersions containing 20% of nimodipine after 4 weeks of storage at +25 °C and 60% rh which are completely opaque samples confirm the presence of nimodipine in the crystalline state. In contrast,

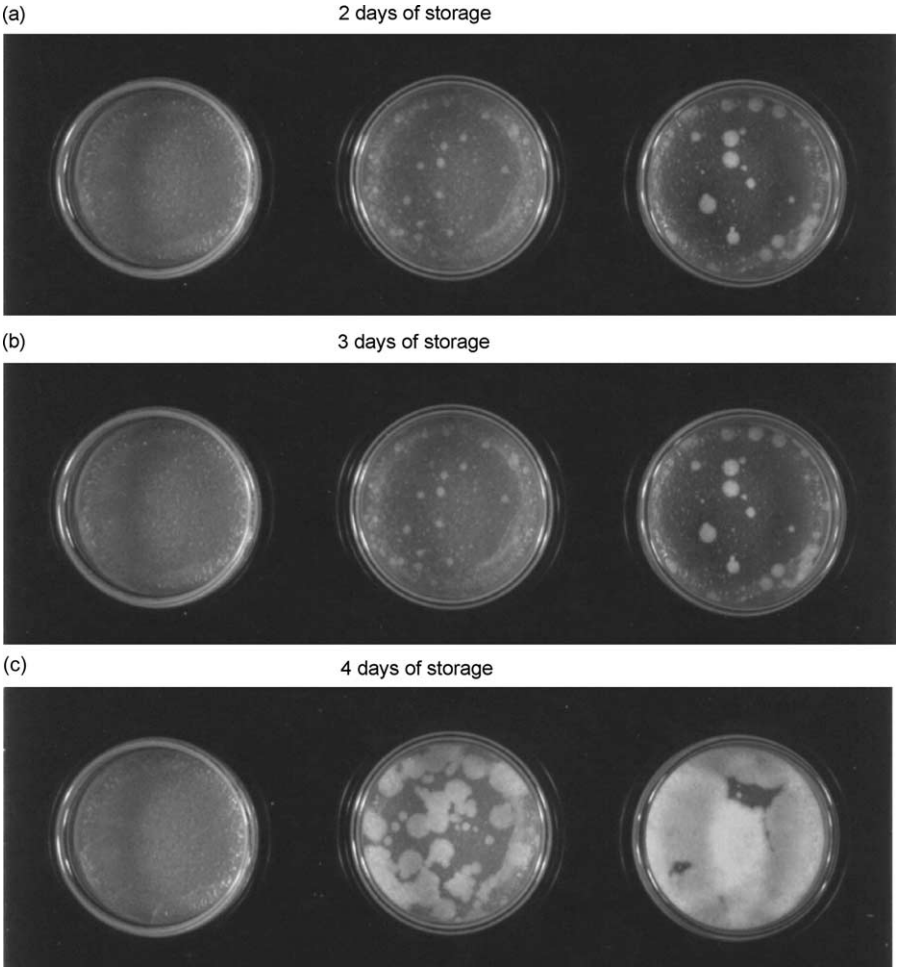

Fig. 10. Photographs of shock frozen solid dispersions containing 20% of nimodipine after 2, 3 and 4 days of storage at −20 °C over silica gel (left hand) or at +25 °C either over silica gel (middle) or at 60% rh (right hand); abbreviations see Table 1.

the diffraction patterns of shock frozen solid dispersions containing 20% nimodipine after 24 h of storage over silica gel at −20 °C which are completely transparent samples do not show any peaks of crystalline nimodipine and correspond to the diffraction pattern of pure polyethylene glycol 2000. Therefore, the extent of opaque areas is indicative for the extent of drug recrystallisation and correlates very well with the dissolution experiments.

4. Conclusion

The dissolution characteristics of nimodipine in water may be improved by the formation of solid dispersions with polyethylene glycol 2000 as carrier by the melting method. However, the absence of crystalline drug material in the solid dispersion is decisive for an increase in solubility as well. In order to obtain solid solutions, where the drug is dissolved within the carrier material, the melted mixture has to be shock frozen, thereby avoiding recrystallisation of the drug during the cooling process.

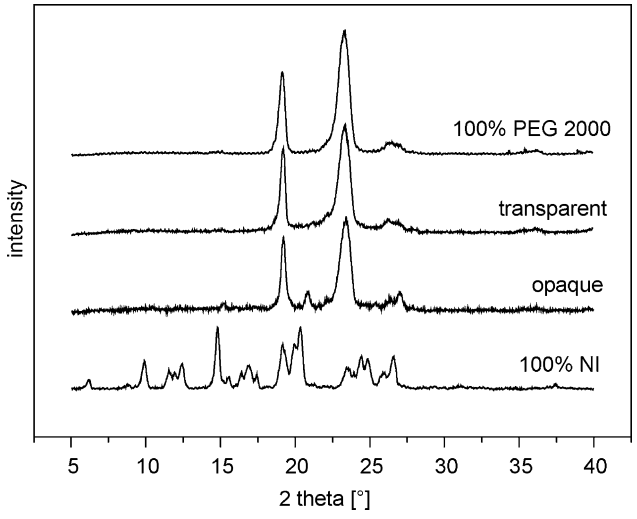

Fig. 11. X-ray diffractograms of shock frozen solid dispersions containing 20% nimodipine after 24 h of storage over silica gel at −20 °C (transparent) and slow cooled solid dispersions containing 20% of nimodipine after 4 weeks of storage at +25 °C and 60% rh (opaque); the first of two measurements is shown. Pure polyethylene glycol 2000 and pure nimodipine are shown as references.

In contrast, slow cooling favours recrystallisation and the development of solid suspensions with unfavourable dissolution properties. As a high cooling rate leads to thermodynamically unstable supersaturated solutions, the conversion into a more stable state is always inherent. Therefore, storage conditions are important for the preservation of the original state. Shock frozen solid dispersions which are stored at elevated temperatures as well as at elevated relative humidities are prone to convert from a supersaturated solid solution into a solid suspension.

In order to get an insight into the physico-chemical properties, that cause the observed differences of the dissolution characteristics, examinations were performed using thermal analysis, X-ray diffraction and macroscopic observation. As experiments by differential scanning calorimetry often fail to detect thermal transitions which cover a wide temperature range, like dissolution processes, or which are connected with the transformation of very small quantities, it is useful to combine this method of thermal analysis with experiments by a hot stage microscope equipped with polarised light, which is superior in the detection of thermal transitions of small quantities of crystalline material. A certain drawback of X-ray diffraction studies is the influence of crystal size and orientation on the area under the diffraction peak which is a measure for the amount of crystalline material. As the size of recrystallised particles in solid dispersions and the orientation of the same cannot be controlled or standardised by sample preparation, a reliable determination of the content of crystalline material is difficult. In this study, simple macroscopic observation of solid dispersions have turned out to be a sensitive tool for the detection and quantification of recrystallised drug material. As recrystallisation of the drug begins, opaque dots appear in the initially homogenous transparent system indicating the emergence of a second phase which turns the initially homogenous into a heterogenous appearance. The extension of the opaque area is dependent only on the amount of recrystallised drug material and is obviously not influenced by crystal size and orientation and therefore, correlates very well with the results obtained from dissolution testing. Taking into account the pros and cons of the various examination methods, only a rational combination of different characterisation methods can be considered as leading to a reliable interpretation of the dissolution profiles.

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