

## Improvement of nifedipine dissolution characteristics using supercritical CO<sub>2</sub><sup>1</sup>

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### Abstract

An application of supercritical fluids (SCFs) for processing of pharmaceuticals is presented. PGSS (Particles from Gas Saturated Solutions), a novel method for high pressure material processing, has been used to improve technological characteristics of the poorly water soluble calcium antagonist nifedipine. Nifedipine was micronized with PGSS and the influence of pre-expansion conditions on the particle size was studied. With PGSS, coprecipitates of nifedipine and PEG 4000 were prepared and evaluated. The solid dispersions had enhanced dissolution rates. The PGSS process shows some advantages over classical methods for solid dispersion preparation. © 1997 Elsevier Science B.V.

**Keywords:** Supercritical fluids; CO<sub>2</sub>; High pressure; Micronization; Nifedipine; PEG 4000

### 1. Introduction

Many drugs possess a poor water solubility and their bioavailabilities are limited by their dissolution rates. Several approaches are known to increase the dissolution rate and hence the bioavailability of such drugs including mi-

cronization, formation of solid dispersions, solvates, adsorbates or complexes. Technologies using supercritical fluids (SCFs) can also be used in this sense.

Beside their extractive, chromatographic and applications in biochemical reactions, supercritical fluids offer interesting applications in material processing. In recent years, processing of pharmaceuticals with SCFs, especially with supercritical carbon dioxide, has received increased attention. Two supercritical micronization techniques have been used to date. In one, particles are formed as

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a result of the rapid expansion of a SC solution. In the other, the SCF is used as an anti-solvent that causes particle precipitation from a liquid solution. The former process is known as rapid expansion of supercritical solution (RESS) and is suitable for substances with sufficient solubility in the SC solvent. The second method is known as gas anti-solvent recrystallization (GASR). The RESS process and its applications to pharmaceutical processes have been reviewed (Phillips and Stella, 1993). Beside being of interest as an alternative to conventional size reduction methods (recently reported also by Allesi et al., 1995) RESS is a novel route to solvent free polymer-drug microspheres and microparticles for the controlled release of drugs (Debenedetti et al., 1993; Tom et al., 1993; Benedetti et al., 1995). The GASR process is of interest in the formation of fine peptide and protein powders (Debenedetti et al., 1993; Tom et al., 1993; Yeo et al., 1993) and polymer microspheres (Benedetti et al., 1995). The possibility of preparing drug loaded polymer microspheres or microparticles by GASR is under investigation (Debenedetti, 1994).

In this work we used a new method for particle generation with SCFs, which so far has not been applied in processing of pharmaceuticals. This method is known as particles from gas saturated solutions (PGSS) (Weidner et al., 1994) and shows some advantages over RESS and GASR processes. When compared with RESS the consumption of CO<sub>2</sub> is an important parameter being lower by an order of magnitude 10<sup>3</sup> for PGSS than for RESS. Since in RESS the substance has to be dissolved in the supercritical gas sufficient solubility in SC CO<sub>2</sub> is the criterion which eliminates many pharmaceutical compounds from RESS consideration. In PGSS on the contrary the compressible gas is dissolved in the compound and this liquid phase is further processed. When compared with GASR advantageously no organic solvent is needed for PGSS.

In this study, the poorly water soluble calcium antagonist nifedipine was used as a model drug and was processed with PGSS with the aim to increase its dissolution rate and hence its bioavailability.

## 2. Experimental

### 2.1. Materials

Crystalline nifedipine, kindly donated by Lek, Slovenia, was used with a melting point of 170°C (Kofler method) and medium particle size of 50 µm.

The carrier was PEG 4000 with a melting point of 57°C, supplied by Hoechst, Germany. CO<sub>2</sub> (99.94%) was donated by Linde plin, Slovenia.

### 2.2. Micronization and preparation of coprecipitates with PGSS

In the PGSS process, a compressible gas (i.e. CO<sub>2</sub>) is dissolved under pressure in a melted substance (or mixture of substances) to be micronized. This gas saturated solution is later expanded, which causes supersaturation and fine particles precipitate. The detailed experimental equipment has been presented (Weidner et al., 1994).

### 2.3. Particle size and particle size distribution

Particle size and particle size distribution were measured with Granulometer Cilas 920, operating on the principle of laser diffraction spectroscopy.

### 2.4. Scanning electron microscopy (SEM)

The shape and surface appearance of particles were observed with a scanning electron microscope (JEOL SM-840 A).

### 2.5. Thermal analyses

A Mettler TA 3000 DSC apparatus was used. All thermal analyses were performed in an inert atmosphere (N<sub>2</sub>). The sample sizes were approximately 10 mg, the heating rate 10 K/min.

### 2.6. Dissolution studies

Dissolution studies were performed following the USP XXII paddle method in 1000 ml of distilled water at 37°C and 100 rpm. Accurately

weighted samples containing the equivalent of 10 mg of nifedipine were spread over the dissolution medium surface. Then, 6 ml aliquots were withdrawn in certain time intervals and passed through a 0.45- $\mu\text{m}$  membrane filter. The withdrawn aliquots were replaced with equal quantities of fresh dissolution medium to maintain a constant volume. The concentrations of nifedipine in the withdrawn samples were determined spectrophotometrically by measuring the absorbance at  $\lambda = 335$  nm using a Perkin Elmer 552 spectrophotometer.

### 2.7. Thin layer chromatography (TLC)

The chemical stability of the micronized samples and coprecipitates was controlled with TLC. Silica gel 60 F<sub>254</sub> TLC plates were used. The samples were dissolved in chloroform, the mobile phase was chloroform/methanol/glacial acetic acid 98:2:0.5 v/v, and the spots were detected at daylight and under an UV light at  $\lambda = 254$  nm.

## 3. Results and discussion

Nifedipine was micronized with the PGSS method. The experiments were carried out in a pre-expansion pressure range from 100–200 bar and at two pre-expansion temperatures, 175 and 185°C. The particle size was reduced from 50 to 15  $\mu\text{m}$  in the best experiments. It was found that

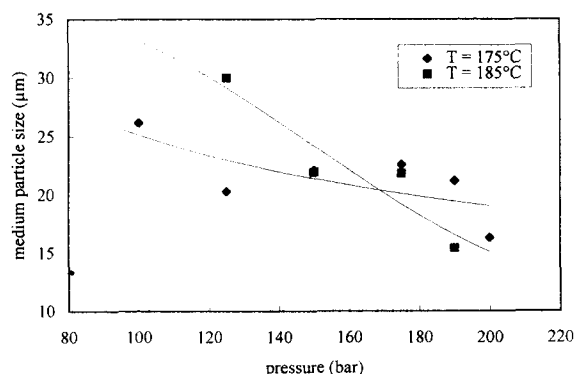


Fig. 1. Influence of pre-expansion pressure on the particle size of micronized nifedipine.



Fig. 2. Particle view of nifedipine before (a) and after PGSS (b) and of a nifedipine-PEG 4000 coprecipitate (c) ( $P = 190$  bar,  $T = 70^\circ\text{C}$ ).

the pre-expansion pressure influences the medium particle size of the micronized nifedipine; this is shown in Fig. 1.

At higher pressures smaller particles were formed. Such results could have been expected since the solubility of  $\text{CO}_2$  in the melt increases

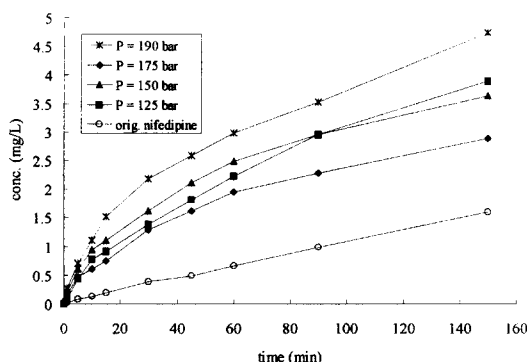


Fig. 3. Dissolution profiles of nifedipine, micronized at 185°C and different pressures compared with original nifedipine.

with increasing pressure (Prausnitz et al., 1986). Consequently during expansion of the liquid phase a higher supersaturation is reached and smaller particles are formed. Such a dependency was shown for PGSS of a mixture of glycerides (Novak et al., 1995).

In Fig. 2a,b, the SEM pictures of nifedipine particles before and after micronization with PGSS are presented. The PGSS process changed the appearance of the particles, which are no more regularly shaped. The spherical parts appearing in the morphology could be due to the simultaneously occurring evaporation of CO<sub>2</sub> from the melt upon expansion on one hand and solidification of the melt caused by the cooling as the compressed gas is expanded on the other hand.

The dissolution studies have shown that mi-

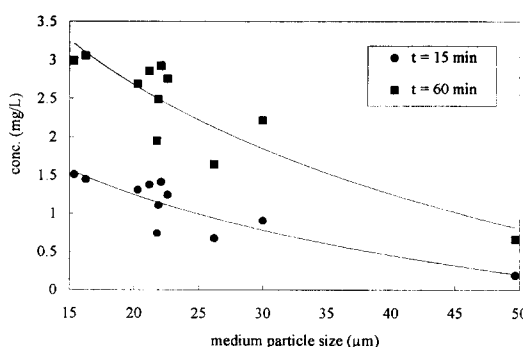


Fig. 4. Concentration of dissolved nifedipine after 15 and 60 min of dissolution as a function of medium particle size.

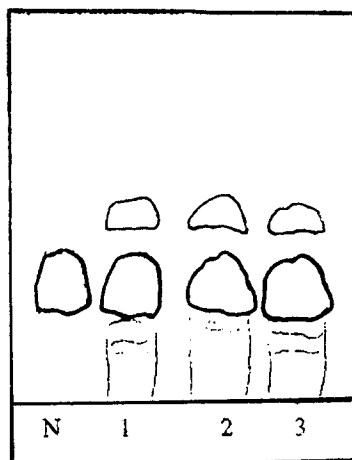


Fig. 5. TLC chromatograms of original nifedipine and micronized samples (N, nifedipine; 1, 2 and 3, micronized nifedipine at different experimental conditions).

cronized nifedipine dissolves faster compared to the original sample what is presented in Fig. 3 for samples, micronized at 185°C and different pre-expansion pressures. The best profile was reached with the highest pre-expansion pressure, 190 bar. For the series of samples, micronized at 175°C, similar results were obtained. In Fig. 4, the dependency between the concentration of the dissolved drug after a certain time of dissolution and the mean particle size is presented. Included are samples, micronized at both pre-expansion temperatures and various pre-expansion pressures as well as original nifedipine with the medium particle size of 50 μm. It can be seen how the amount of the dissolved drug increases as the particle size decreases.

With the particle size reduction the dissolution rate increased to some extent, but the anticipated effective surface area was probably reduced by the drug's hydrophobicity and agglomeration of the particles during micronization.

TLC and DSC analyses showed that some chemical changes occurred during nifedipine processing with PGSS. On the TLC chromatograms of all micronized samples some new spots were observed. In Fig. 5, the rather intense spots of nitrosophenylpyridine analogue, a degradation product of nifedipine, can be seen above the

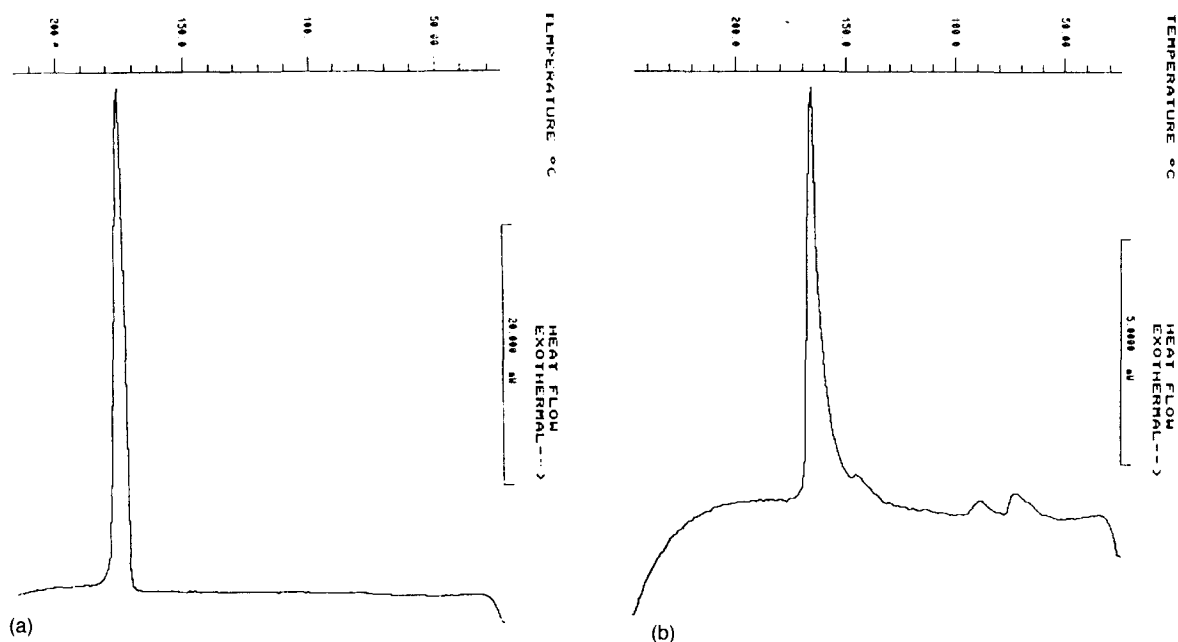


Fig. 6. DSC scans of original nifedipine (a) and a micronized sample (b) ( $P = 200$  bar,  $T = 175^{\circ}\text{C}$ ).

nifedipine spots. DSC scans of original and micronized nifedipine are presented in Fig. 6. On the scan of the micronized sample some new peaks appeared below the melting peak of nifedipine ( $170^{\circ}\text{C}$ ). The changed DSC scan could be in connection with the appearance of the degradation products. The peak of nitrosophenylpyridine analogue may be seen as the melting peak of the pure substance is at  $95^{\circ}\text{C}$  (Thoma and Kerker, 1992). It is possible that the nitrophenylpyridine analogue and the azoksi derivative of nifedipine are present in the micronized sample as well since they are believed to be the degradation products of the nitrosophenylpyridine analogue when exposed to high temperatures (Thoma and Kerker, 1992). For nifedipine, it is known to undergo degradation when exposed to sunlight or UV light. The degradation in our experiments was probably due to high temperatures ( $175$  and  $185^{\circ}\text{C}$ ) the drug was exposed to during micronization with PGSS.

In order to find a possibility of carrying out the PGSS process under milder conditions (a lower pre-expansion temperature) to avoid degradation

of nifedipine on one hand and to further increase its dissolution rate on the other hand it was searched for a suitable carrier. It was found that addition of certain amounts of the hydrophilic polymer PEG 4000 to nifedipine results in a melting point decrease. The system with 20% nifedipine and 80% PEG 4000 showed only one melting peak at about  $55^{\circ}\text{C}$  (Fig. 7b).

In the same way as nifedipine alone mixtures of nifedipine and PEG 4000 were micronized with PGSS to obtain coprecipitates. Experiments were carried out at pre-expansion pressures between 120 and 190 bar and temperatures between 50 and  $70^{\circ}\text{C}$ . The composition of the mixture was 20% nifedipine and 80% PEG 4000 (1:4). Fine powdered coprecipitates were obtained.

On the TLC chromatograms of coprecipitates no new spots appeared; on the DSC scan (Fig. 7c) just the melting peak of the coprecipitate was observed thus indicating that no degradation of nifedipine occurred under mentioned conditions of PGSS.

In Fig. 2c, a SEM picture of a coprecipitate is presented. Similarly as for nifedipine alone the

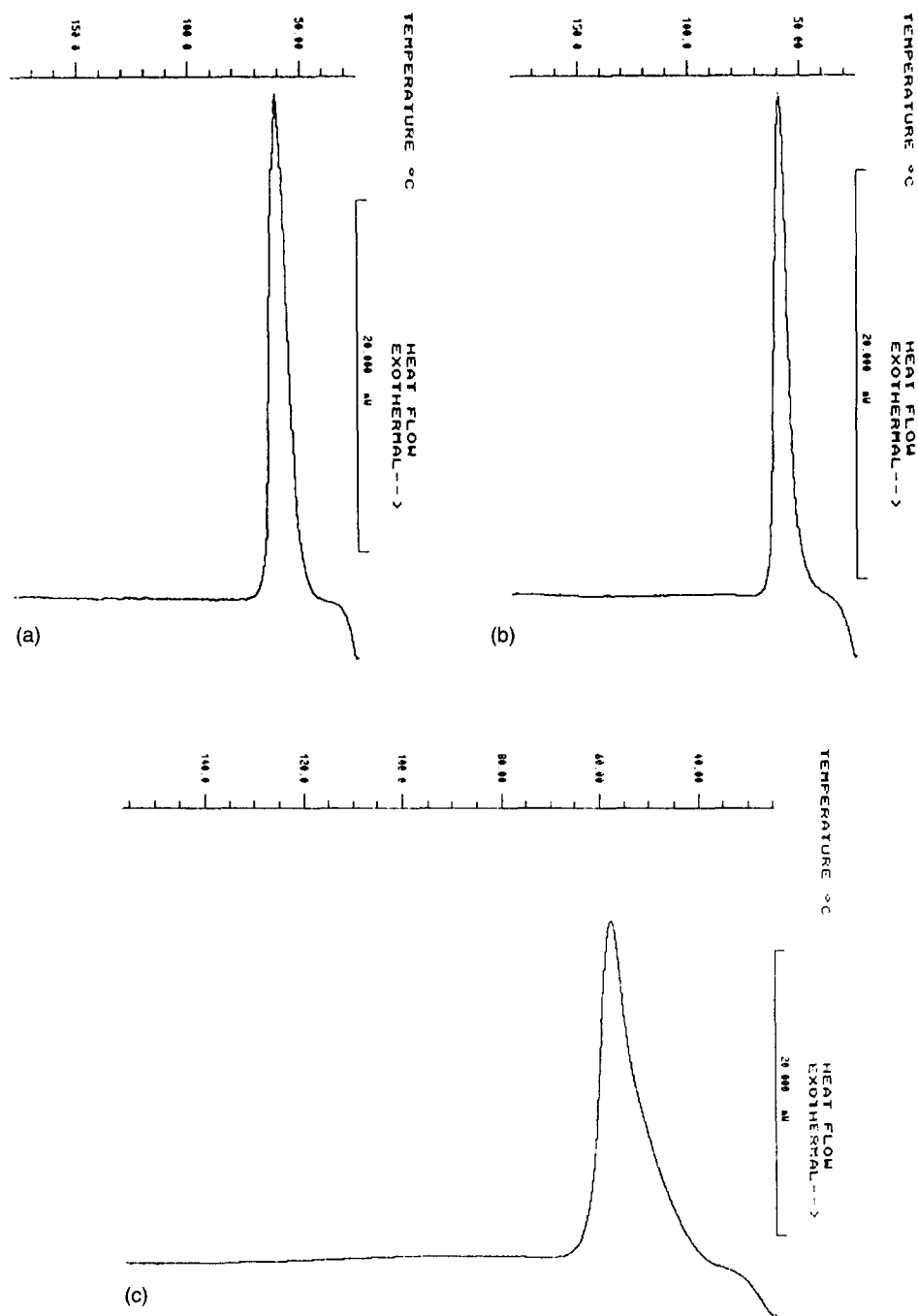


Fig. 7. DSC scans of PEG 4000 (a), a mixture containing 20% of nifedipine and 80% of PEG 4000 (b), and a nifedipine-PEG 4000 coprecipitate (c) ( $P = 190$  bar,  $T = 70^{\circ}\text{C}$ ).

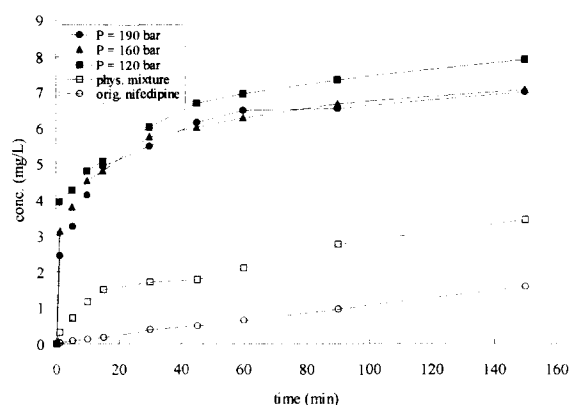


Fig. 8. Dissolution profiles of coprecipitates prepared at 50°C and different pre-expansion pressures compared with original nifedipine and physical mixture of the same composition (1:4).

non-regular shape of the coprecipitate obtained by PGSS with the bubble-like parts can be observed. From the morphology could be suggested that the structure of the coprecipitate particles may be porous.

Dissolution studies showed that the dissolution rates of nifedipine-PEG 4000 solid dispersions had increased. In Fig. 8, dissolution profiles of solid dispersions, prepared at 50°C and different pre-expansion pressures are presented and in Fig. 9 those of coprecipitates, prepared at 190 bar and different pre-expansion temperatures are shown. On an average a 9-times higher amount of the

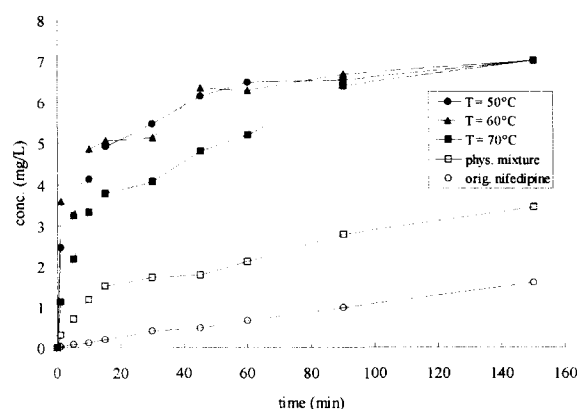


Fig. 9. Dissolution profiles of coprecipitates prepared at 190 bar and different pre-expansion temperatures compared with original nifedipine and physical mixture of the same composition (1:4).

drug dissolved in 1 h from solid dispersions compared to original nifedipine.

From Fig. 8 it can be seen that the pre-expansion pressure hardly influences the dissolution behavior of nifedipine coprecipitates. The same was observed for other pre-expansion temperatures. Even at 120 bar enough CO<sub>2</sub> dissolves in the melt to cause a rapid precipitation of the components. The influence of pre-expansion temperature on the dissolution is shown in Fig. 9 at 190 bar and the results were similar at other pre-expansion pressures. The slightly slower dissolution of coprecipitates prepared at highest temperature (70°C) could be explained with the decreased solubility of CO<sub>2</sub> in the melt at a higher temperature (Prausnitz et al., 1986).

The mechanism of the enhanced dissolution rate of drugs in form of solid dispersions was interpreted by different authors (for example, Sugimoto et al., 1980; Ford, 1986; Sumnu, 1986). We believe that a combination of factors including particle size reduction, certain interactions between nifedipine and PEG 4000 and the possible solubilization effect of the hydrophilic carrier contributed to the enhanced dissolution rates of solid dispersions.

With the PGSS process we prepared solid dispersions in a new way, which has some advantages over classical methods of solid dispersion preparation, namely the fusion (or melting) methods and the solvent processes. In the PGSS process there is a melt of the drug and carrier, saturated with supercritical CO<sub>2</sub>. Upon expansion this solution is rapidly cooled down and the solid dispersion precipitates in form of microparticles, thereby avoiding the comminution step. Since the cooling is rapid due to the expansion of CO<sub>2</sub> present fine particles with a narrow particle size distribution can be formed. On the other hand, there is no organic solvent needed. Carbon dioxide is an inert gas at atmospheric pressure. Especially the removal of the solvent is a problem of classical coprecipitation or coevaporation techniques. Large amounts of organic solvents are needed, it is hard to find their optimal removal rate and a complete removal of the solvent is often a long and difficult process (Ford, 1986). With PGSS, coprecipitates in powder form can be obtained in one step.

#### 4. Conclusion

In spite of the intensive research work the use of supercritical fluids in processing of pharmaceuticals is still at the elementary stage. Two high pressure micronization techniques, RESS and GASR have been used to date for pharmaceutical applications. In this work PGSS, a novel method for material processing with SCFs has been applied for improving the technological characteristics of a drug for the first time. Micronization of nifedipine with PGSS resulted in reducing the particle size from 50 to 15  $\mu\text{m}$  (at 190 bar). The process caused degradation of nifedipine, which was probably due to high temperatures (175 and 185°C). With PGSS of nifedipine and PEG 4000 (1:4) coprecipitates were prepared at different experimental conditions. Even pre-expansion pressure of 120 bar and temperature of 50°C are suitable for preparing nifedipine-PEG 4000 solid dispersions with enhanced dissolution rates and no degradation products. Since PGSS gave solvent free coprecipitates in powdered form in one step it shows some advantages over classical methods for solid dispersion preparation. The PGSS process may provide different interesting applications in pharmaceutical technology.

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