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Solid-state characterization of nifedipine solid dispersions

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Abstract

The purpose of this study is to characterize the nature and solid-state properties of a solid dispersion system of nifedipine (33.3% w/w) in a polymer matrix consisting of Pluronic F68 (33.3% w/w) and Gelucire 50/13 (33.3% w/w). The nature of nifedipine dispersed in the matrix was studied by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC) and diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). The rate and extent of water uptake of the solid dispersion were determined by weight gain. The dissolution rate of nifedipine solid dispersion was determined using Apparatus 2 of USP XXIII (1995). Quantitative PXRD showed that the saturation solubility of nifedipine in the polymer matrix is 2.1–3.0% w/w and indicated an excess of crystalline nifedipine in the solid dispersion. The maximum water uptake by the solid dispersion exposed to 75% RH at 45 °C was 3.3 times higher than for the dispersion exposed to 65% RH at 25 °C. Over 8 weeks, PXRD and DRIFTS of the nifedipine matrix stored at 25 or 4 °C were unchanged, showing constancy of crystallinity and intermolecular interactions. For a given mass of nifedipine (20 mg) and for a given particle size of nifedipine (< 850 μm), the initial release rate of nifedipine from the solid dispersion was faster (46.2% of the nifedipine dissolved in 20 min) than that of the pure drug (1.2% of the nifedipine dissolved in 20 min). The results indicate that the nifedipine solid dispersion is physically stable over 8 weeks. Nifedipine is released faster from the solid dispersion than from the pure crystalline drug of the same particle size.

Keywords: Solid dispersion; Nifedipine; Pluronic F68; Gelucire 50/13; Solubility; Dissolution rate

1. Introduction

Nifedipine (4-(2-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine; Scheme 1), is a calcium channel blocking agent that is used to treat a variety of cardiovascular disorders, such as angina pectoris and hypertension. Nifedipine exists in the form of yellow crystals of melting point

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172–174 °C. A commercial product of nifedipine is Adalat®, an extended-release formulation containing 20 mg of nifedipine (Maggi et al., 1996). Nifedipine has been shown to exist in three monotropically related modifications, modification I (m.p. 169–173 °C), which is the thermodynamically stable modification at room temperature, mod. II (m.p. 161–163 °C) and mod. III (m.p. 135 °C), which are metastable modifications (Eckert and Müller, 1977; Burger and Koller, 1996). Four different 1,4-dioxane solvates (A–D) of nifedipine have also been crystallized and are easily distinguishable using thermomicroscopy, differential scanning calorimetry (DSC) and infrared (IR) spectroscopy (Burger and Koller, 1996).

Due to its low aqueous solubility, nifedipine often shows low and irregular bioavailability after oral administration (Pabst et al., 1986; Ali, 1989). The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. The solid dispersion of poorly water-soluble drugs in water-soluble surface-active and self-emulsifying carriers enhances drug dissolution and bioavailability (Chiou and Riegelman, 1970, 1971a,b; Stupak and Bates, 1972; Vila-Jato and Alonso, 1986; Sjökvist et al., 1992; Serajuddin, 1999). An important mechanism is the reduction of the drug's particle size to the microcrystalline or molecular level for rapid dissolution and absorption.

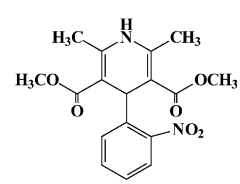
The microcrystalline state of the drug in a water-soluble carrier may be achieved by complete solubilization of the desired dose of the drug in the carrier matrix at an elevated temperature followed by crystallization of the drug, and possible crystallization of the matrix components, on cooling. Hence, the choice of a water-soluble carrier is important in the preparation of a stable solid dispersion.

The preparation and characterization of solid dispersions of nifedipine have been reported previously. The solid dispersions of nifedipine in carriers, such as polyethylene glycol (PEG) 6000 (Lin and Cham, 1996) and polyvinylpyrrolidone (Sugimoto et al., 1980), have been developed to increase drug absorption. Solid dispersions of nifedipine in PEG and phosphatidylcholine dissolve faster than the solid drug, which was attributed to the formation of lipid vesicles that entrapped a certain concentration of nifedipine (Law et al., 1992). Cogrinding of nifedipine with PEG 6000 + hydroxypropyl methylcellulose also improved nifedipine dissolution (Sugimoto et al., 1998).

In this paper, we report the preparation and characterization of nifedipine solid dispersions in a new polymeric matrix system containing 1:1 proportions of Pluronic F68 and Gelucire 50/13. A preliminary report of the present work was presented as a poster at the 2000 AAPS Annual Meeting (Vippagunta et al., 2000). Unless otherwise stated, all ratios and percentages are expressed as w/w. The desired dose of nifedipine (33.3% w/w) forms a uniform solid dispersion in the polymeric matrix consisting of 1:1 Pluronic F68 and Gelucire 50/13 polymeric matrix.

To avoid frequent repetition of long phrases, we abbreviate the compositions of the prepared materials as follows: the drug-free solid dispersion consisting of Pluronic F68 and Gelucire 50/13 (1:1) (**D**); the solid dispersion (1:1:1) containing nifedipine (33.3%) in a matrix consisting of Pluronic F68 (33.3%) and Gelucire 50/13 (33.3%) (**ND**) prepared by slow cooling of the fused mixture; and the physical mixture (1:1:1) consisting of nifedipine (33.3%), Pluronic F68 (33.3%) and Gelucire 50/13 (33.3%) (**NM**).

Pluronic F68, also known as Poloxamer 188, is a nonionic polyoxyethylene-polyoxypropylene block copolymer ($HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$, where $a = 80$ and $b = 27$) (Collett and Weller, 1994), used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. The polyoxyethylene segment of the Pluronic is relatively hydrophilic, while the polyoxypropylene segment is relatively hydrophobic. The Pluronics have received increas-



Scheme 1. Molecular structure of nifedipine.

ing application in the formulation of dosage forms owing to their low toxicity and ability to form a clear solution or gel in aqueous media, thus solubilizing many water insoluble compounds essentially by the formation of micelles (Lin and Kawashima, 1985).

Gelucires are a group of glyceride-based excipients, composed of mixtures of mono-, di- and triglycerides with PEG esters of fatty acid and are classified by two numbers, the first referring to the approximate melting point of the base and the second to the hydrophile–lypophile balance (HLB) value (Sutananta et al., 1994). The nature and proportion of the components in the Gelucires determine the hydrophobicity and drug release properties of the corresponding dosage forms (Craig, 1995). Gelucires are widely used as controlled release matrices. For example, various poorly water soluble compounds, such as triamterene or temazepam (Dordunoo et al., 1991), theophylline (Sutananta et al., 1995) and cinnarizine (Ginés et al., 1995), have been prepared as solid dispersions in Gelucires.

The specific aims of this study are to determine (a) the crystallinity and polymorphic and/or pseudopolymorphic form of nifedipine in a polymeric matrix consisting of 1:1 Pluronic F68 and Gelucire 50/13, using powder X-ray diffractometry (PXRD) and differential scanning calorimetry (DSC); (b) the nature of the interactions between nifedipine and the constituents of the polymeric matrix using diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS); (c) the physical stability of nifedipine in the matrix systems as a function of time, temperature and relative humidity; and (d) the dissolution profile of nifedipine from solid dispersions compared to that of nifedipine alone.

2. Materials and methods

2.1. Materials

Nifedipine, Pluronic F68 and Gelucire 50/13 were supplied by EM Industries Inc., Hawthorne, NY. All solvents used were of analytical grade. The nifedipine used to prepare the formulations was in the form of a fine powder. Because nifedipine is sensitive to light, all experiments were performed under subdued light.

2.2. Preparation of solid dispersions

Nifedipine solid dispersions, consisting of various proportions of nifedipine in a mixture of Pluronic F68 and Gelucire 50/13 (1:1) matrix system, were prepared as described below. In order to determine the solid solubility of nifedipine in Pluronic F68 and Gelucire 50/13 (1:1) matrix by PXRD, the following solid dispersions (nifedipine proportion stated first) were prepared: 1:1:1 (33.3% nifedipine) corresponding to **ND** defined above; 0.75:1:1 (27.2% nifedipine); 0.5:1:1 (20.0% nifedipine); 0.25:1:1 (11.1% nifedipine); 0.15:1:1 (6.97% nifedpine); 0.1:1:1 (4.76% nifedipine); 0.075:1:1 (3.61% nifedipine); 0.065:1:1 (3.15% nifedipine), 0.05:1:1 (2.44% nifedipine); and 0:1:1 (0% nifedipine) drug-free dispersion, corresponding to **D** defined above.

The solid dispersions were prepared by the melt (fusion) method as follows. Physical mixtures of Pluronic F68 (1.0 g) and Gelucire 50/13 (1.0 g) were heated while stirring in a water bath maintained at 70 °C. To each fused mixture, an appropriate weight of nifedipine powder was added to produce the required proportion. The mixture was then stirred for 1 h at 70 °C until all the nifedipine had dissolved and was uniformly dispersed in the matrix. The fused mixture was allowed to cool slowly to room temperature with stirring. The solid dispersions were then dried for ≈ 24 h in a desiccator over calcium sulfate (Drierite™, W.A. Hammond Drierite Co., Xenia, OH) at room temperature. The solidified melts were then sieved (20 mesh, ≤ 850 μm) and stored in amber-colored glass bottles at room temperature.

A solid dispersion containing nifedipine (33.3%), Pluronic F68 and Gelucire 50/13 (1:1:1) was prepared as described above, but the fused mixture was quenched rapidly by placing the glass container in a mixture of ice and salt, instead of being slowly cooled, corresponding to the method used for **ND**.

Physical mixtures of equal weights of Pluronic F68 and Gelucire 50/13 with different weights of free crystalline nifedipine were prepared by simple geometric mixing of the three pure solid components with a spatula followed by sieving through a No. 20 mesh sieve (≤ 850 μm). The composition of these physical mixtures correspond to those of the solid dispersions (matrices) defined above.

2.3. Powder X-ray diffractometry (PXRD)

PXRD patterns of each of the pure ingredients and all of the solid dispersions containing varying proportions of nifedipine in the Pluronic F68 and Gelucire 50/13 (1:1) matrix were recorded using an X-ray diffractometer (Bruker AXS or Siemens D5005) with Ni filtered CuKα line as the source of radiation. For quantitative studies, the angular range 5–40° 2θ was scanned with a step size of 0.05° 2θ and a dwell time of 1.0 s at each step. The 2θ values and the intensities of the peaks were compared for both pure ingredients and solid dispersion systems.

To determine the solid solubility of nifedipine in Pluronic F68 and Gelucire 50/13 matrix by quantitative PXRD, three batches of solid dispersions containing 11.1, 20 and 33.3% w/w of nifedipine in Pluronic F68 and Gelucire 50/13 (1:1) were prepared. The drug-free solid dispersion (**D**) was employed as a negative control. A fixed weight (225 mg) of each formulation was poured into an aluminum sample holder using the 'sideways filling' technique (Suryanarayanan, 1990) to reduce preferred orientation. For the quantitative analysis, two X-ray peaks characteristic of nifedipine were chosen in the range 9–13° 2θ. This range was scanned with a step size of 0.01° 2θ and a dwell time of 1.0 s at each step. The peak area, after appropriate background subtraction, was evaluated by integration from 9.5° to 11° 2θ for Peak 1 (10.3° 2θ corresponding to a d-spacing of 8.51 Å) and from 11 to 12.5° 2θ for Peak 2 (11.9° 2θ corresponding to a d-spacing of 7.4 Å). The drug-free solid dispersion (**D**), employed as a control, did not exhibit any peaks in the range 9–13° 2θ.

2.4. Differential scanning calorimetry (DSC)

A DuPont differential scanning calorimeter (model 910, TA instruments, New Castle, DE) was used to obtain the DSC curves representing the rates of heat uptake with respect to temperature. About 3 mg of sample was weighed in a standard open aluminum pan. An empty pan of the same type was utilized as the reference. Samples were heated from 20 to 200 °C at a heating rate of 10 °C/min, while being purged with dry nitrogen. Calibrations of temperature and heat flow were performed with indium.

2.5. Diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS)

The Fourier-transformed infrared (FTIR) spectra of samples were obtained, after appropriate background subtraction, using an FTIR spectrometer (Series II Magna 750, Nicollet Instrument Corp., Madison, WI) equipped with a deuterated triglycine sulfate (DTGS) detector, a diffuse reflectance accessory and a data station. About 1–2 mg of the sample was mixed with dry potassium bromide and the sample was scanned from 400 and 4000 cm^{-1}.

2.6. Stability studies

About 200 mg of each of the solid dispersions was weighed into a glass vial. The samples were stored in a refrigerator (4 °C) or at room temperature (25 °C), each for 1 week or 2 months. After storage under each of these four conditions, the PXRD patterns of all the solid dispersions were recorded.

Sealed desiccators containing saturated salt solutions were equilibrated at 65% RH and 25 °C or at 75% RH and 45 °C. About 100 mg of each of the solid dispersions ($n = 3$) containing 0, 3.61 and 33.3% nifedipine in Pluronic F68 and Gelucire 50/13 (1:1) matrix and the corresponding physical mixture (**NM**), were placed in the sealed desiccators. At defined intervals of time, the samples were removed from the desiccators and weighed. The samples were covered during weighing to reduce direct exposure to the external at-

mosphere. After the period of time (≈ 68 h) required for apparent sorption equilibrium, as evidenced by constant weight, the samples were subjected to PXRD to detect any phase change due to water sorption.

2.7. Solubility measurements

Solubility measurements were carried out by adding either 40 mg of pure nifedipine or 120.12 mg of solid dispersion **ND**, or physical mixture **NM**, each containing 40 mg of nifedipine, to 40 ml of simulated gastric fluid containing methanol (0.2% v/v). Because nifedipine is not completely soluble in simulated gastric fluid even at low concentrations, a better solvent, such as methanol, needs to be added to the dissolution medium to maintain sink conditions. In order to reduce evaporation of the solvent, which leads to variability of the dissolution results and to provide a more discriminating dissolution medium, a minimal concentration of methanol (0.2% v/v) was added to the dissolution medium. The suspensions were magnetically stirred at 37 °C in a dark room for 48 h, at the end of which samples were withdrawn and filtered through 0.45 μm membrane filters. The filtrates were suitably diluted and analyzed spectrophotometrically at $\lambda_{max} = 340$ nm. The results of triplicate measurements and their means were reported.

2.8. Dissolution studies

The dissolution of nifedipine alone, nifedipine from the physical mixture **NM** and nifedipine from the solid dispersion **ND** were determined using Apparatus No. 2 of the USP XXIII (1995). The dissolution medium consisted of simulated gastric fluid USP (without enzymes) containing methanol (0.2% v/v) maintained at 37 °C. Samples equivalent to 20 mg of nifedipine was added to 900 ml of dissolution medium in a 1000-ml cylindrical beaker. A two-blade stirrer centrally placed 20 cm from the bottom of the beaker provided stirring at 50 rpm. At suitable time intervals (5, 10 or 15 min), 5.0 and 3.0 ml samples were withdrawn over a period of 2 h. The same volume of preheated dissolution medium was infused into the medium after each sample was taken in order to maintain a constant volume of the dissolution medium throughout the test. The samples were filtered (pore size 0.45 μm) and the nifedipine content was determined spectrophotometrically at $\lambda_{max} = 340$ nm. All experiments were carried out in triplicate and the results presented are the mean values of the three experiments; the error bars represent the S.D.

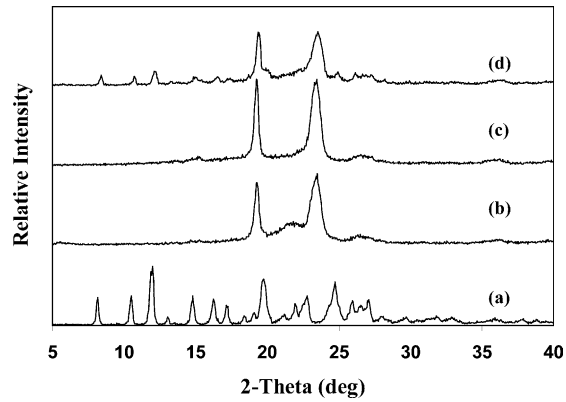


Fig. 1. X-ray powder diffraction patterns of (a) pure nifedipine, (b) neat Pluronic F68, (c) neat Gelucire 50/13 and (d) solid dispersion of nifedipine (33.3% w/w) in Pluronic F68 and Gelucire 50/13 matrix (1:1:1) (**ND**).

3. Results and discussion

3.1. Solid-state characterization

The PXRD patterns of pure nifedipine, neat Pluronic F68, neat Gelucire 50/13 and the solid dispersion **ND** are shown in Fig. 1. The powder X-ray diffractogram of pure nifedipine drug powder from 5 to 20° 2θ (Fig. 1a) showed numerous distinctive peaks that indicated a high crystallinity. Pluronic F68 and Gelucire 50/13 also exhibited some crystallinity, as indicated by the two peaks of high intensity (at 19.25° and 23.45° 2θ for Pluronic F68 and at 19.26° and 23.50° 2θ for Gelucire 50/13) and other peaks of lower intensity (Fig. 1b, c, respectively). Sutananta et al. (1994) have shown that the glycerides present in Gelucires exhibit complex crystallization behav-

ior, which may effect the product performance of the dosage forms. The two intense peaks mentioned above, in the PXRD pattern of Gelucire, may be attributed to the crystalline glycerides in the sample. The PXRD pattern of the solid dispersion **ND** (Fig. 1d) exhibits all the characteristic diffraction peaks of Pluronic F68, Gelucire 50/13 and crystalline nifedipine, but of lower intensity. This study reveals that some nifedipine still exists in the crystalline state in the solid dispersion and that, at this concentration (33.3%), the proportion of the drug may equal or exceed its solid solubility. The same result was given by the solid dispersion of the same composition, but prepared by rapid cooling in a mixture of ice and salt. The actual percentage of crystalline nifedipine, determined by quantitative PXRD, is stated near the end of Section 3.2.

Fig. 2 shows the DSC curves for pure nifedipine, neat Pluronic F68, neat Gelucire 50/13, drug-free solid dispersion **D**, physical mixture **NM** and solid dispersion **ND**. Pure nifedipine exhibits a sharp melting endotherm at 175.1 °C (Fig. 2a). Pluronic F68 exhibited a single sharp melting endotherm at 56.8 °C (Fig. 2b), whereas Gelucire 50/13 showed a broad melting endotherm at 48.5 °C (Fig. 2c). The drug-free dispersion **D**, prepared by the fusion method, exhibited a sharp endotherm at 54.9 °C and a small endotherm at 40.3 °C (Fig. 2d). The sharp melting endotherms observed indicate the partial crystallinity of this drug-free dispersion. Also, the melting points of both Pluronic F68 and Gelucire 50/13 decreased after preparation of the solidified melt, suggesting the formation of a eutectic.

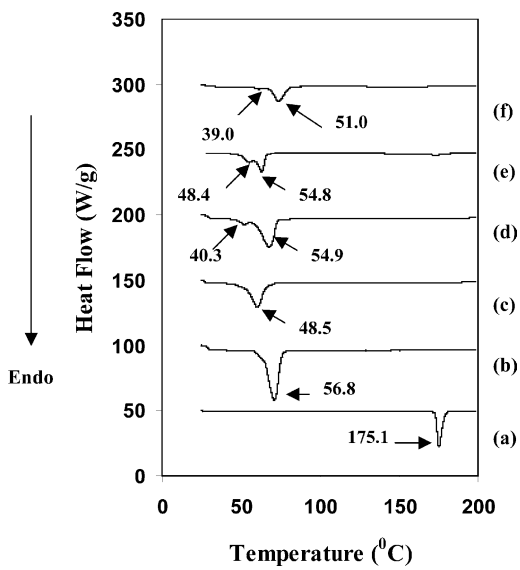


Fig. 2. DSC curves in open pans for (a) pure nifedipine, (b) neat Pluronic F68, (c) neat Gelucire 50/13, (d) drug-free solid dispersion containing Pluronic F68 and Gelucire 50/13 (1:1) (**D**), (e) physical mixture of nifedipine (33.3% w/w), Pluronic F68 and Gelucire 50/13 (1:1:1) (**NM**) and (f) solid dispersion consisting of nifedipine (33.3% w/w), Pluronic F68 and Gelucire 50/13 (1:1:1) (**ND**).

The physical mixture (**NM**) exhibited a sharp endotherm at 54.8 °C, corresponding to the melting of Pluronic F68 and a shoulder endotherm at 48.4 °C, corresponding to the melting of Gelucire 50/13 (Fig. 2e). The weak broad endotherm between 138.8 and 182.0 °C may be attributed to the melting of undissolved crystalline nifedipine in the matrix. The solid dispersion (**ND**) exhibited two melting endotherms, a sharp one at 51 °C and a small one at 39 °C. No endotherm corresponding to the melting of pure crystalline nifedipine was observed. These results suggest that on heating in DSC, nifedipine progressively dissolves in Pluronic F68 and Gelucire 50/13 and dissolves completely below the melting temperature of crystalline nifedipine. Other solid dispersions have been found to behave similarly. Examples include: the solid dispersion of triamterene in PEG and Gelucire 44/14, in which triamterene forms monotectics with both polymers (Dordunoo et al., 1991); the solid dispersion of cinnarizine in Gelucire 53/10, in which no melting peak of cinnarizine was observed at low concentrations ($\leq 30\%$ w/w) (Ginés et al., 1995); and the solid dispersion of paracetamol in PEG 4000, where again there was evidence of monotectic behavior (Lloyd et al., 1997). Craig (1990) has previously suggested that the drug may dissolve in the molten polymer, such as PEG, over a wide range of temperature; hence the melting endotherm of the drug broadens to such an extent as to be indistinguishable from the baseline. The data presented here largely supports this hypothesis. Therefore, DSC appears to be unsuitable for determining the degree of crystallinity and/or the

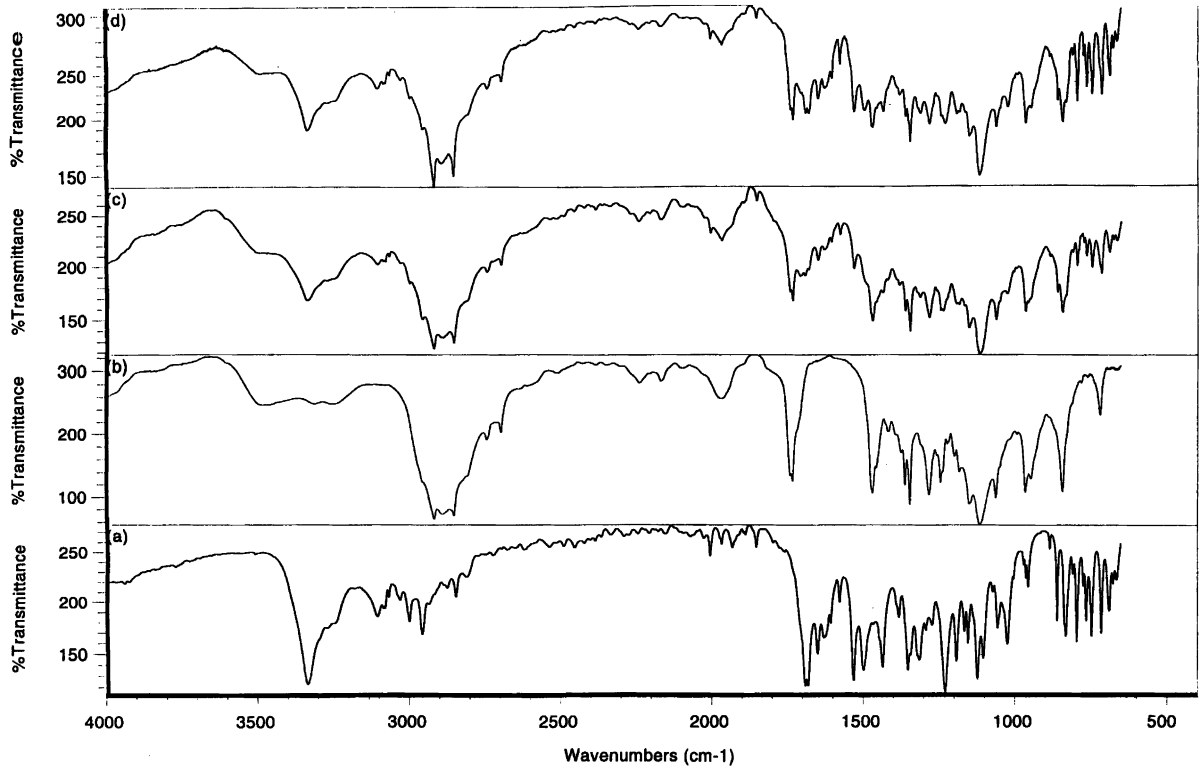


Fig. 3. FTIR spectra of (a) pure nifedipine, (b) drug-free solid dispersion containing Pluronic F68 and Gelucire 50/13 (1:1) (**D**), (c) physical mixture of nifedipine (33.3% w/w), Pluronic F68 and Gelucire 50/13 (1:1:1) (**NM**) and (d) solid dispersion consisting of nifedipine (33.3% w/w), Pluronic F68 and Gelucire 50/13 (1:1:1) (**ND**).

solubility of the drug in the solid dispersion system at ambient temperature.

In order to further ascertain whether nifedipine undergoes a polymorphic change during the preparation of the solid dispersion and to test for possible intermolecular interactions between nifedipine and the constituents of the dispersion matrix, DRIFTS was used (Fig. 3). Nifedipine powder exhibits sharp peaks in the FTIR spectrum indicating its crystalline nature (Fig. 3a). Because the individual FTIR spectra of Pluronic F68 and Gelucire 50/13 are very similar, they are not presented. The drug-free solid dispersion **D** exhibits relatively broad peaks due to the large molecular sizes of Pluronic F68 and Gelucire 50/13 and their partially amorphous nature (Fig. 3b). For physical mixture (**NM**) a peak characteristic of the N–H stretching vibration of nifedipine was observed at 33.332 cm^{-1} (Fig. 3c). A similar peak was also observed in the corresponding solid dispersion (**ND**) (Fig. 3d). The absence of any other new peaks in the solid dispersions indicates that nifedipine is not undergoing any polymorphic change during their preparation, confirming the PXRD results. Furthermore, the absence of shifts in the wavenumbers of the FTIR peaks of the solid dispersion (**ND**) (Fig. 3d) compared to the physical mixture (**NM**) (Fig. 3c) indicates lack of significant interaction between the drug and the components in the solid dispersion.

3.2. Determination of the solid-state solubility of nifedipine in the solid dispersion

The PXRD patterns of nifedipine solid dispersions in Pluronic F68 and Gelucire 50/13 (1:1), containing varying concentrations of nifedipine (Fig. 4) show the characteristic peaks of Pluronic

F68 and Gelucire 50/13. These PXRD patterns obtained were compared with those of physical mixtures containing the same proportions of nifedipine. The characteristic peaks of nifedipine (8.2°, 10.6° and 11.9° 2θ) gradually increase with increasing nifedipine concentration in the solid dispersions.

The solid dispersions containing $\geq 4.76\%$ w/w nifedipine exhibited peaks corresponding to crystalline nifedipine. In the solid dispersions containing $\leq 3.6\%$ nifedipine, the characteristic diffraction peaks of nifedipine were not observed, indicating that the crystalline characteristics of nifedipine had disappeared in these solid dispersions. Nifedipine at low concentrations may have either converted to a metastable amorphous form or may have dissolved in the matrix system to form a solid solution, or may exist in a microcrystalline form in the matrix system. It is also possible that the detection limit of the technique ($\leq 5\%$) has been reached. The results indicate that the saturation solubility of nifedipine in the solid dispersion consisting of Pluronic F68 and Gelucire 50/13 (1:1) is about $\leq 3.6\%$ w/w, corresponding to the upper limit of the solid solubility of nifedipine present as a solid solution in the polymeric matrix.

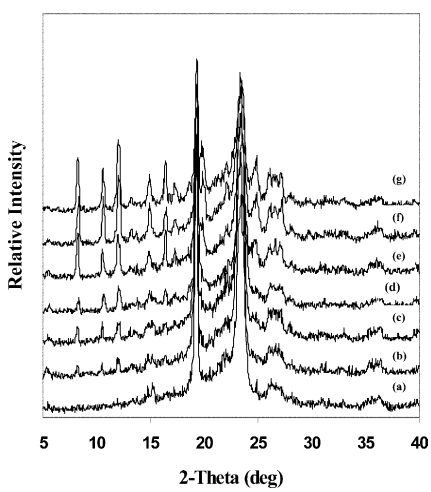


Fig. 4. X-ray powder diffraction patterns of solid dispersions containing (a) 3.61%, (b) 4.76%, (c) 6.97%, (d) 11.1%, (e) 20.0%, (f) 27.2% and (g) 33.3% w/w nifedipine (**ND**) in Pluronic F68 and Gelucire 50/13 (1:1) matrix.

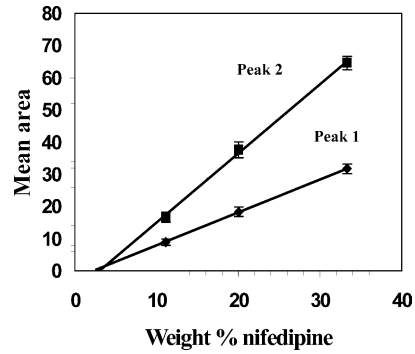


Fig. 5. Plot of the mean area ($n = 3$) of the X-ray powder diffraction peaks as a function of weight percent nifedipine in the solid dispersions consisting of 11.1, 20.0 and 33.3% w/w nifedipine (**ND**) in Pluronic F68 and Gelucire 50/13 (1:1) matrix. (●) Peak 1, 10.3° 2θ, (■) Peak 2, 11.9° 2θ.

From quantitative PXRD, the mean peak areas of the two peaks characteristic of nifedipine (Peak 1, 10.3° 2θ; Peak 2, 11.9° 2θ) are plotted against the weight percent of nifedipine in the solid dispersions in Fig. 5. The intercept on the horizontal axis (between 2.17 and 3.02% w/w) provides an estimate of the ambient solid solubility of nifedipine in the solid dispersion system consisting of Pluronic F68 and Gelucire 50/13 (1:1). Using PXRD, Law et al. (1992) determined the solid state solubility of nifedipine in PEG 4000 to be in the range 1–5% w/w. However, Lin and Cham (1996) suggested that nifedipine is present in the amorphous state in PEG 6000 because they did not observe any crystalline nifedipine peaks up to 10% w/w. Due to the difficulty in differentiating between a drug in the amorphous state and a drug in the solid solution, the latter interpretation is placed on the results of the present work. In fact, any drug molecules that are molecularly dispersed in solid solution in the amorphous matrix must necessarily be present in an amorphous state. Hence, we deduce that the solid solubility of nifedipine in Pluronic F68 and Gelucire 50/13 (1:1) solid dispersions is 2.17–3.02% w/w. The remaining nifedipine, 97–98% w/w remains in the crystalline state. The S.D. in the determinations of peak area using PXRD ranged from 1.0 to 2.5%.

The major objective of this study was to determine the physical state of nifedipine in the polymeric matrix consisting of 1:1 Pluronic F68 and

Gelucire 50/13 on complete melting and cooling. The qualitative and quantitative PXRD results clearly indicate that nifedipine is present predominantly in the crystalline state in the polymeric matrix. Hence, phase changes that are critical to stability, such as changes in the dissolution rate as a result of crystallization of the amorphous form of drug, are unlikely to pose problems for these formulations.

3.3. Effect of temperature and relative humidity on the physical stability of nifedipine solid dispersion over time

Fig. 6 shows the PXRD of solid dispersions containing nifedipine (33.3%) in Pluronic F68 and Gelucire 50/13 (1:1:1) matrix (**ND**), freshly prepared and stored at 25 or 4 °C for 1 week or 2 months. No new peaks are observed in the diffraction patterns of the solid dispersions after storage under these conditions indicating that neither the drug nor the matrix system underwent any phase change. Also, no shift in the peak positions is observed indicating no interaction between the drug and the polymeric matrix during storage. Furthermore, no significant increase in peak intensities corresponding to crystalline

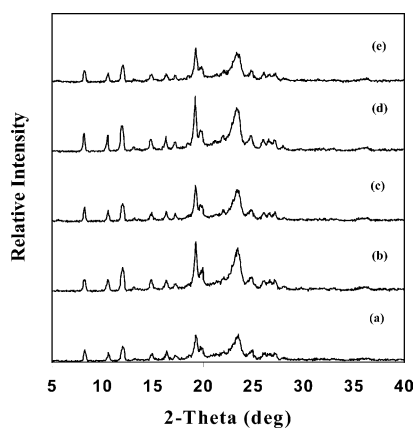


Fig. 6. X-ray powder diffraction patterns of solid dispersions containing nifedipine (33.3% w/w) in Pluronic F68 and Gelucire 50/13 (1:1) matrix (**ND**) determined after storage under the following conditions: (a) freshly prepare, (b) stored at 25 °C for 1 week, (c) stored at 25 °C for 2 months, (d) stored at 4 °C for 1 week and (e) stored at 4 °C for 2 months.

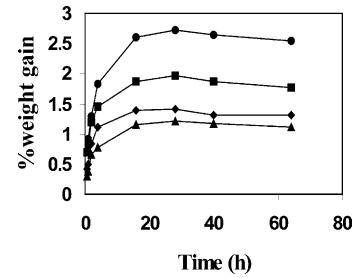


Fig. 7. Percentage weight gain versus time of exposure to 65% RH at 25 °C for solid dispersions containing (■) 0% (**D**), (●) 3.6%, (◆) 33.3% w/w nifedipine in Pluronic F68 and Gelucire 50/13 (1:1) matrix (**ND**) and (▲) physical mixture of nifedipine (33.3% w/w), Pluronic F68 and Gelucire 50/13 (1:1:1) (**NM**).

nifedipine is observed for solid dispersions stored at 4 °C and at room temperature, suggesting that there is no significant increase in the amount of crystalline nifedipine in the matrix system within 2 months. Because the solid state solubility data have indicated that ≈ 97–98% of the drug is in the crystalline form in the matrix, it is not surprising to see no significant increase in the intensity of the peaks characteristic of the crystalline drug. The diffractograms of the solid dispersions showed no loss nor gain of peaks, indicating the essential chemical and physical stability of the dispersion at room temperature and at 4 °C during the period of the study.

Upon exposure to 65% RH at 25 °C (Fig. 7), or 75% RH at 45 °C (Fig. 8), the rate and extent

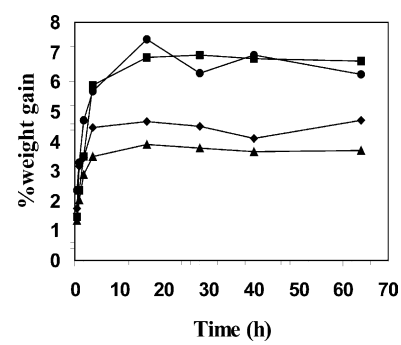


Fig. 8. Percentage weight gain versus time of exposure to 75% RH at 45 °C for solid dispersions containing (■) 0% (**D**), (●) 3.6%, (◆) 33.3% w/w nifedipine in Pluronic F68 and Gelucire 50/13 (1:1) matrix (**ND**) and (▲) physical mixture of nifedipine (33.3% w/w), Pluronic F68 and Gelucire 50/13 (1:1:1) (**NM**).

of water uptake of solid dispersions containing 0, 3.61 and 33.3% w/w nifedipine in Pluronic F68 and Gelucire 50/13 (1:1) and of the physical mixture **NM** (1:1:1), were each determined by plotting the weight gain as a function of time. The physical (phase) stability of these materials on water uptake was monitored using PXRD.

The maximum water uptake is found to be: 1.90% for dispersions containing 0% nifedipine, **D**, 2.70% for solid dispersions containing 3.61% nifedipine; 1.4% for solid dispersions containing 33.3% nifedipine, **ND**, and 1.20% for the physical mixture containing 33.3% nifedipine, **NM**. The increased water uptake for solid dispersions containing 3.61 and 0% nifedipine may be attributed to the greater proportion of both Pluronic F68 and Gelucire 50/13, which can form hydrogen bonds with the water molecules sorbed from the vapor. However, the Pluronics generally contain $< 0.5\%$ w/w water and are hygroscopic only at high relative humidities ($> 80\%$). With passage of time, following the maximum water uptake, a loss in weight was observed for all samples. This behavior suggests that the ingredients in the dispersions, as well as in the physical mixture, are crystallizing on uptake of water. It has been suggested that slow cooling facilitates fractional crystallization of the components of Gelucire into segregated regions (Sutananta et al., 1994). It is therefore possible that the presence of moisture in the dispersions facilitates the segregation process, resulting in the crystallization of the drug and the carrier. A study of the solid dispersions of theophylline in Gelucire base has shown that Gelucires undergo structural alterations on exposure to high humidities, the extent of the changes being highly dependent on the chemical compositions of the base (Sutananta et al., 1996).

For all the solid dispersions and the physical mixture (**NM**), the equilibrium (maximum) moisture uptake is achieved after ≈ 30 h on exposure to 75% RH and 45 °C (Fig. 8) and is greater than that after exposure to 65% RH at 25 °CC (Fig. 7) by a factor of ≈ 3.3. The equilibrium (maximum) moisture uptake was found to decrease with increasing proportions of nifedipine, a hydrophobic drug, under both conditions of RH and temperature (Figs. 7 and 8). For all the solid dispersions, the equilibrium (maximum) moisture uptake and the rate of its attainment are $> 75\%$ RH and 45 °C (Fig. 8) than at 65% RH and 25 °C (Fig. 7).

During exposure to 75% RH at 45 °C for > 16 h, liquification of the samples was observed. In explanation, the melting point of Pluronic F68 and Gelucire 50/13 constituting the dispersion system is lowered by the sorbed water resulting in the melting of the samples at ambient temperature or the sorbed water dissolves the dispersion. Important considerations in the use of Gelucires in dosage forms are the effects of humidity on their structure and drug release properties. While glycerides are not in themselves hygroscopic, the presence of the PEG stearates in the Gelucires may facilitate an interaction with water. Hence, the chemical composition of the Gelucires may determine the behavior of the base on storage at elevated humidities (Sutananta et al., 1996). Therefore, it may not be advisable to conduct accelerated stability studies on solid dispersions prepared from low melting excipients.

The PXRD patterns of the dispersion systems and physical mixture (**NM**) when exposed to 65% RH at 25 °C or at 75% RH at 45 °C, did not show any gain or loss of peaks, suggesting the absence of polymorphic changes and indicating their physical and chemical stability. Solid dispersions containing 33.3% nifedipine (**ND**) exhibited a slight increase in the nifedipine peak areas, which may be attributed to an increase either in the degree of crystallinity or in the size of the nifedipine particles or both.

3.4. Solubility and dissolution studies

The solubility of nifedipine from the dispersion system (**ND**) and from the physical mixture (**NM**) in simulated gastric fluid containing methanol (0.2% v/v) at 37 °C is greater than that of the pure drug by a factor of ≈ 2.0 (Table 1). Pluronic F68 and Gelucire 50/13 may enhance the solubility of nifedipine either by micellar solubilization or by reducing the activity coefficient of the drug by reducing the hydrophobic interaction or by both processes. In addition, improvement of the wetting of the hydrophobic nifedipine crystals may occur.

Table 1
Solubility ($n = 3$) of pure nifedipine, nifedipine from a physical mixture of nifedipine, Pluronic F68 and Gelucire 50/13 (1:1:1) (**NM**) and nifedipine from a solid dispersion consisting of nifedipine, Pluronic F68 and Gelucire 50/13 (1:1:1) (**ND**), in simulated gastric fluid containing methanol (0.2% v/v) at 37 °C

Solid containing nifedipine	Solubility at 37 °C (μg/ml) in simulated gastric fluid containing methanol (0.2% v/v)			
	After 48 h measured			Mean ± S.D.
Pure nifedipine	12.58	13.41	13.83	13.28 ± 0.64
Physical mixture of nifedipine, Pluronic F68 and Gelucire 50/13 (1:1:1) (**NM**)	23.52	23.05	23.64	23.40 ± 0.31
Solid dispersion consisting of nifedipine (33.3%), Pluronic F68 and Gelucire 50/13 (1:1:1) (**ND**)	24.69	26.75	26.53	26.00 ± 1.13

The physical mixture (**NM**) and the solid dispersion (**ND**) exhibited significantly faster initial dissolution rates than the pure drug (Fig. 9). Serajuddin et al. (1988) and Smith et al. (1990) showed that Gelucires with high HLB values may be used to obtain fast release of drugs. From the physical mixture (**NM**) a burst release of ≈8–11% of nifedipine is observed within the first 15–20 min followed by slow release of nifedipine into the dissolution medium. The initial increase in the dissolution of the drug when physically mixed with Pluronic F68 and Gelucire 50/13 is probably attributable to an improvement of wetting and to local solubilization by the excipient in the diffusion layer.

Within the first 20 min, the solid dispersion (**ND**) exhibited a higher burst release of ≈46% of nifedipine. The initial increase in dissolution of nifedipine from the solid dispersion (**ND**) may be attributed to factors such as the absence of aggregation, a reduction in the particle size of the drug in the matrix and an increase in the solubility of the drug in the presence of the excipients, Pluronic F68 and Gelucire 50/13. Similar observations have been reported for solid dispersions of naproxen in PEG 4000, 6000 and 20,000 (Mura et al., 1996). After 30 min, little or no additional increase in the dissolution of nifedipine indicated the attainment of saturation. The attainment of saturation before 100% release of the drug from the solid dispersion (**ND**) or the physical mixture (**NM**) may be attributed to the fast dissolution of water soluble polymeric matrix in the medium, leaving behind a high concentration of nifedipine particles, resulting in saturation of the dissolution medium with respect to nifedipine concentration.

4. Conclusions

DSC of nifedipine solid dispersions in Pluronic F68 and Gelucire 50/13 and of the corresponding physical mixture did not indicate the presence of crystalline nifedipine because nifedipine dissolved completely below its melting point. However, PXRD of nifedipine solid dispersions indicated the presence of appreciable proportions of crystalline nifedipine. Therefore, DSC is not recommended for determining free crystals or the degree of crystallinity. PXRD and FTIR indicated that nifedipine did not undergo any polymorphic change during the preparation of the solid dispersions.

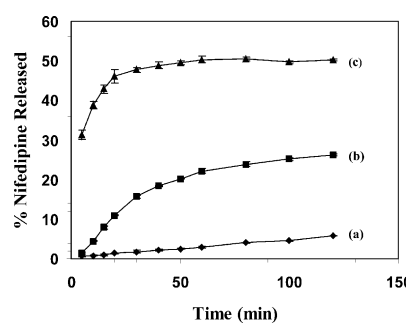


Fig. 9. Dissolution profiles for (a) pure nifedipine, (b) physical mixture of nifedipine (33.3% w/w), Pluronic F68 and Gelucire 50/13 (1:1:1) (**NM**) and (c) solid dispersion of nifedipine (33.3% w/w) in Pluronic F68: Gelucire 50/13 matrix (1:1:1) (**ND**).

Quantitative PXRD showed that the solid solubility of nifedipine in a dispersion system consisting of Pluronic F68 and Gelucire 50/13 (1:1) lies between 2.17 and 3.02% w/w. PXRD also showed the essential stability of the solid dispersions on storage at room temperature and at 4 °C for 2 months. The equilibrium (maximum) value and the rate of water uptake for solid dispersions increased with decreasing nifedipine content and were greater during exposure to 75% RH at 45 °C than to 65% RH at 25 °C. The samples exposed to 75% RH at 45 °C for more than 16 h, underwent liquification. Hence, it may not be advisable to conduct accelerated stability studies on solid dispersions prepared from a low melting excipient. Solid dispersion of nifedipine in Pluronic F68 and Gelucire 50/13 (1:1) improves the dissolution of nifedipine compared to the corresponding physical mixture or to the pure drug crystals.

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