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Physical properties and dissolution behaviour of nifedipine/mannitol solid dispersions prepared by hot melt method

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Abstract

Solid dispersions of nifedipine (NIF) with mannitol in preparations containing 10 and 50% (w/w) of drug were manufactured by the hot melt method. Physical properties and the dissolution behaviour of binary systems as physical mixtures and solid dispersions were investigated. In all samples, the crystal structure of NIF was confirmed using differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). Fourier transform infrared spectroscopy (FTIR) revealed, there was no interaction between drug and carrier, however, FTIR spectra indicated formation of thermodynamically less stable polymorph of mannitol. The dissolution rate of NIF from solid dispersions was markedly enhanced, the effect being stronger at higher drug loading (50%, w/w, NIF). The dissolution rate enhancement was attributed to improved wetting of NIF crystals due to mannitol particles, attached on the surface, as inspected by means of SEM. Thermal stability of NIF, mannitol and two other potential carbohydrate carriers (lactose and saccharose) during the hot melt procedure was investigated using ^{1}H NMR. NIF was found to be thermically stable under conditions applied. As expected, among carriers only mannitol demonstrated suitable resistance to high temperature used in experiments.

Keywords: Nifedipine; Mannitol; Solid dispersion; Hot melt method; ^{1}H NMR

1. Introduction

Bioavailability of poorly water-soluble drugs that undergo dissolution rate-limited gastrointestinal absorption, can generally be improved by formulation techniques, such as preparation of solid dispersions

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(Leuner and Dressman, 2000). From the first extensive review (Chiou and Riegelman, 1971; Ford, 1986), number of papers on studies comprising variety of carriers, drug/carrier ratios and methods of preparation has been published. Solid dispersed systems can be obtained by hot melt or solvent method. Because of toxicity and ecological problems associated with the use of organic solvents, hot melt approach represents the advantageous means of solid dispersion preparation, where only thermostable components are relevant.

Although having relatively high-melting point (166–168 °C) (Armstrong and Reier, 2000), mannitol has been investigated and successfully employed in the hot melt procedure as a carrier for improving drug solubilization (Arias et al., 1995). It is a highly water-soluble compound with low toxicity, negligible caloric value and low hygroscopicity. Lately, it has been designated as unsuitable for preparation of solid dispersions because of its polymorphic transition that may occur after melting (Gombás et al., 2003). However, energy/temperature diagram exhibits only small differences between thermodynamically stable (I) and metastable modification (II) (Burger et al., 2000).

Nifedipine (NIF), 1,4-dihydropyridine with calcium channel blocking activity, has poor aqueous solubility (Syed Laik, 1989), resulting in low and often irregular bioavailability. Attempts to incorporate the NIF into the water-soluble matrix, such as polyvinylpyrrolidone (Sugimoto et al., 1981), polyethylene glycol (Law et al., 1992; Lin and Cham, 1996), phosphatidylcholine (Yamamura and Rogers, 1996), chitosan and chitosan glutamate (Portero et al., 1998), hydroxypropylmethylcellulose (Cilurzo et al., 2002) and mixture of Pluronic F68 and Gelucire 50/13 (Vippagunta et al., 2002) have been made, resulting in strongly improved dissolution rate. The studies of physical properties mostly demonstrated the presence of disordered structure, which significantly contributed to dissolution characteristics.

The aim of our investigations was to obtain solid dispersions of NIF and mannitol with more favourable drug dissolution profiles. Some of the physicochemical properties have been studied and an attempt to connect them with dissolution behaviour has been made. Additionally, the stability of NIF and several carbohydrate carriers (mannitol, lactose and saccharose) during solid dispersion preparation has been established using solution nuclear magnetic resonance (NMR).

2. Materials and methods

2.1. Materials

Nifedipine, mannitol and lactose were supplied by Lek Pharmaceutical d.d. (Slovenia). Saccharose was purchased from Sigma–Aldrich (Germany).

2.2. Preparation of samples

When exposed to light, nifedipine decomposes to nitroso- and nitro-derivative (Budvári-Bárány et al., 1990), therefore all procedures were carried out under light-protected conditions.

2.2.1. Physical mixtures

Previously sieved ($\leq$160 μm) NIF and mannitol in a drug:carrier ratio 1:9 (10%, w/w, nifedipine) and 1:1 (50%, w/w, NIF) were accurately weighed. Physical mixtures were obtained by blending the components in a mortar.

2.2.2. Solid dispersions

Solid dispersions containing 10 and 50% (w/w) NIF were prepared by hot melt method. Corresponding physical mixtures were heated in an oil bath at 175 °C until they melted. Solidification was reached by cooling to room temperature under ambient conditions. Afterwards, the mixture was pulverised, sieved, and the fraction $\leq$160 μm was selected.

2.3. Differential-scanning calorimetry (DSC)

Samples were heated on a Pyris 1 DSC (Perkin Elmer, USA) equipped with Intracooler 2P cooling accessory. Accurately weighed samples (5–10 mg) were placed in standard aluminium pans and covered with a pierced lid. Heating rate of 5 K/min was used with a nitrogen purge of 20 ml/min.

2.4. FTIR spectroscopy

Infrared analysis was performed using Nicolet Nexus (Nicolet Instrument Co., USA) equipped with an InGaAs detector and an ATR Smart DuraSamplIR sampling accessory. Data were acquired using OMNIC software (version 5.2, Nicolet Instrument Co.). MID spectra were measured over the range 4000–400 cm^{-1}

with an instrument resolution of 4 cm^{-1}. Each individual spectrum was an average of 32 scans.

2.5. NMR studies

Stability of NIF and carriers during solid dispersion preparation was analysed by means of nuclear magnetic resonance (Bruker Avance DPX_{300}). Spectra were recorded at 300 MHz with dimethyl sulfoxide as a solvent and tetramethylsilane as an internal standard. Spectra were assigned according to chemical shift rules and coupling patterns. Two-dimensional NMR experiments GS-COSY and GS-HMQC were also performed.

2.6. Scanning electron microscopy

Morphology of the NIF/mannitol systems was investigated using a JEOL T220 Scanning Microscope (Jeol, Japan). Beforehand, the samples were sputter-coated with gold for 5 min using a vacuum evaporator Balzers SCD 050 (Balzers, Liechtenstein).

2.7. Dissolution studies

Dissolution studies of NIF from powdered samples were performed using the USP XXV paddle method (VanKel 7000 Dissolution test station, USA) with a stirring speed of 100 rpm. Phosphate buffer solution with pH 6.8 containing 0.5 % sodium lauryl sulphate was used as a dissolution medium, assuring sink conditions ($C < 0.15C_S$). Samples containing 10 mg of NIF were spread onto the surface of 900 ml of dissolution medium at 37.0 ± 0.5 °C. At appropriate time intervals, aliquots of 10 ml were withdrawn and measured spectrophotometrically (UV Spectrophotometer 8453, Hewlett Packard, Germany) at $\lambda = 238$ nm. Experiments were carried out in triplicate, therefore only mean values with S.D. error bars are reported.

3. Results and discussion

The thermal stability of carbohydrate carriers during the hot melt process was determined by NMR spectroscopy. From ^{1}H NMR spectra we observed that, after the procedure of solid dispersion preparation, mannitol remained virtually unchanged, while the treatment of lactose and saccharose resulted in 85% and 13–15% degradation, respectively. For this reason, we only used mannitol for further investigation. As we were interested in the chemical mechanisms of carbohydrate degradation, we also performed two-dimensional NMR experiments GS-COSY and GS-HMQC. In the case of lactose, a molecule of water was eliminated from the structure with the consequent formation of the double bond. Since saccharose lacks a free anomeric hydroxy group, its stability is higher, the cleavage of a glycosidic bond was the first step of degradation. Nevertheless, stability of lactose can be improved with chemical modifications in its structure. The only derivative tested to date was peracetyllactose, which was superior in the view of stability; however, the low-water solubility precludes its use as a carrier for solid dispersions.

NMR-spectroscopy was also used for determining the stability of nifedipine. The ^{1}H-spectra of nifedipine and mannitol before temperature treatment and the mixture of both compounds in approximately 1:1 ratio (50% w/w NIF) after the hot melt process are presented in Fig. 1. The integrals and chemical shifts remained unchanged, showing that the method is nondestructive for the substances tested.

Molar volumes of NIF and mannitol are 272.2 ± 3.0 and 114.1 ± 3.0 cm^3, respectively. Molar volumes were calculated using the ACD ChemScetch 3.5 program. It was established that in the case of antidiabetic agent with similar molar volume (279.1 ± 3.0 cm^3), for the improvement of dissolution behaviour the amount of mannitol should be at least three times the weight of the drug (i.e. 25%, w/w of drug), if the mixture is prepared as a co-grounded powder (Kubo and Mizobe, 1997). In our case, we decided to use a mixture with a drug portion of 10% (w/w), which resulted in drug/carrier molar ratio approximately 1:17 (i.e. 5.5% mol/mol NIF). Taking into account molar volumes, this should satisfy the condition of solid solution formation, but the influence of mutual miscibility is by all means significant, as proved by the following results.

DSC curves in Fig. 2 revealed that both mannitol and NIF exhibited an endothermic peak with the onset temperature of 166.6 and 172.9 °C, respectively. These melting peaks indicated the crystalline nature of both components as received. Thermograms of 10 and 50% (w/w) solid dispersions suggest crystal habit of NIF in both samples. From the comparison of DSC traces for 10% (w/w) mixtures, reduction of peak area for NIF

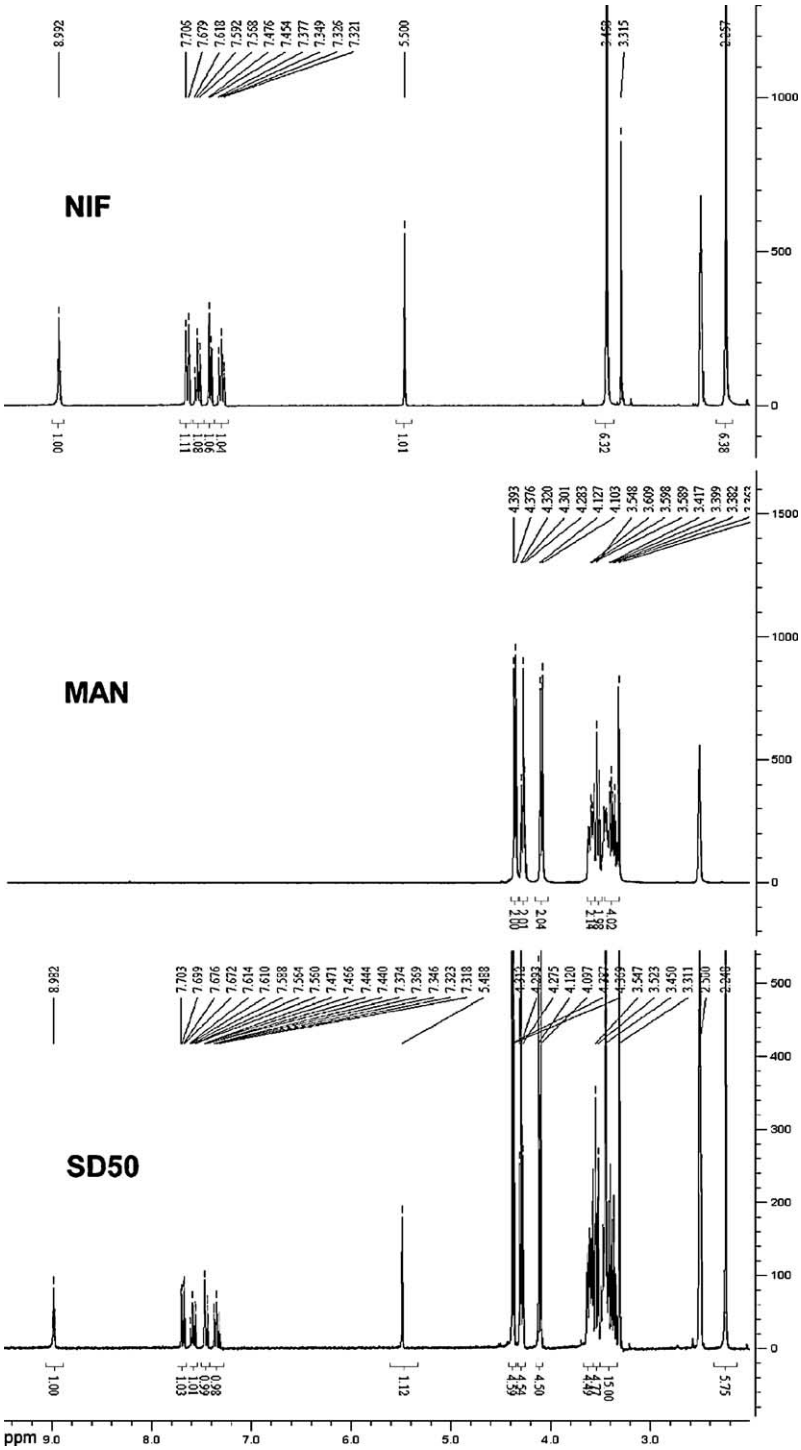

Fig. 1. ^{1}H NMR spectra of untreated nifedipine (NIF), untreated mannitol (MAN) and the 50% (w/w) solid dispersion (SD50) prepared by hot melt process.

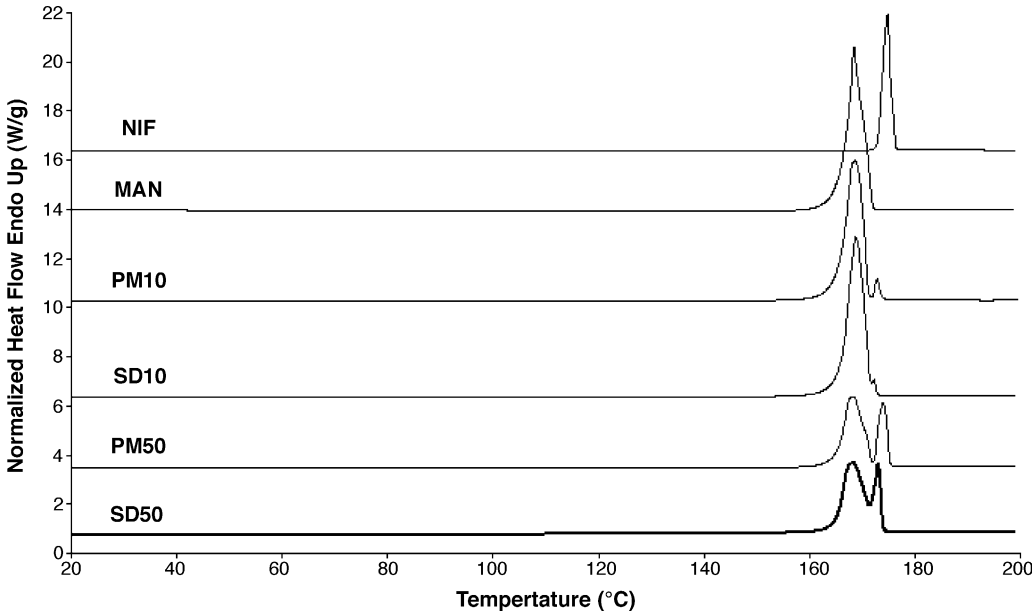

Fig. 2. DSC curves of NIF, mannitol (MAN) and their binary systems (PM: physical mixtures and SD: solid dispersions), containing 10 and 50% (w/w) of drug.

can be observed in the dispersed system. This indicates partial dissolution of NIF in the molten carrier. There were no shifts of onset temperatures in the binary mixtures. For NIF, the values were between 171.8 and 172.3 °C, whereas mannitol melted at 165.3–166.0 °C.

The FTIR spectra in the transmittance mode are depicted in Fig. 3. Pure NIF displays a peak characteristic of the N–H stretching vibration and a band with main peak at 1675 cm^{-1} indicative of the C=O stretch of the esteric group. As the proportion of NIF in the blend decreases, the latter becomes less expressive. In the solid dispersions, neither form changes nor shifts were observed for C=O stretching band. In the mixtures, N–H peak was overlapped with O–H signal of mannitol, which formed a broad band around 3270 cm^{-1}. From these results, it was concluded there were no intermolecular interactions between the drug and the carrier. In the solid dispersions, peak of asymmetric C–H vibrational stretching of mannitol between 2880 and 3000 cm^{-1} distinctively changes. This indicates that mannitol in the original form, as well as in the physical mixtures, existed in the thermodynamically stable modification (modification I) (Burger et al., 2000). The SD preparation caused the formation of thermodynamically less stable modification II, which is monotropically related to modification I.

The morphology of the NIF/mannitol systems prepared by the melting method was studied by means of SEM. Micrographs of solid dispersions (Fig. 4b and d) exhibited different arrangement between the drug and the carrier in comparison with physical mixtures (Fig. 4a and c). In solid dispersions, particles of mannitol were attached onto the surface of NIF crystals. They were also considerably smaller than in the case of physical mixture, while NIF particles had approximately equal size.

Solid dispersions and physical mixtures were tested for dissolution properties and compared with pure crystalline NIF. The results in Fig. 5 show that dissolution of drug from physical mixtures was significantly improved, but the solid dispersion formation resulted in a marked increase of NIF dissolution comparing to physical mixtures. The percentage of NIF dissolved after 15 min (D_{15}) and the characteristic time for 50%-dissolution of NIF initial amount ($t_{50\%}$) were calculated (Table 1). Formation of 10 and 50% (w/w) solid dispersions decreased the $t_{50\%}$ value from 50.9 min (pure NIF) to 5.3 and 11.8 min, respectively. After 15 min,

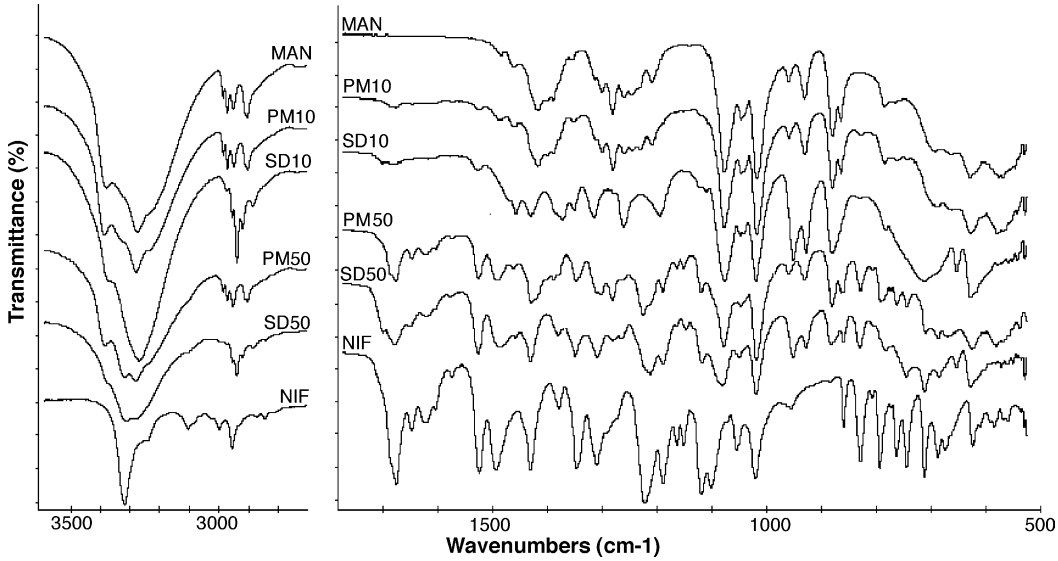

Fig. 3. FTIR spectra of pure nifedipine (NIF), mannitol (MAN), physical mixtures and solid dispersions (PM and SD, respectively) containing 10 and 50% (w/w) of nifedipine.

there were almost 60 and 53% of drug dissolved from both types of solid dispersions, respectively, while the NIF alone resulted in only 19% dissolution. $t_{50\%}$ decreased with the percentage of NIF in solid dispersions, which is in agreement with other systems with mannitol (Arias et al., 1995).

Typical mechanisms for improvement of dissolution characteristics of drugs via solid dispersions are

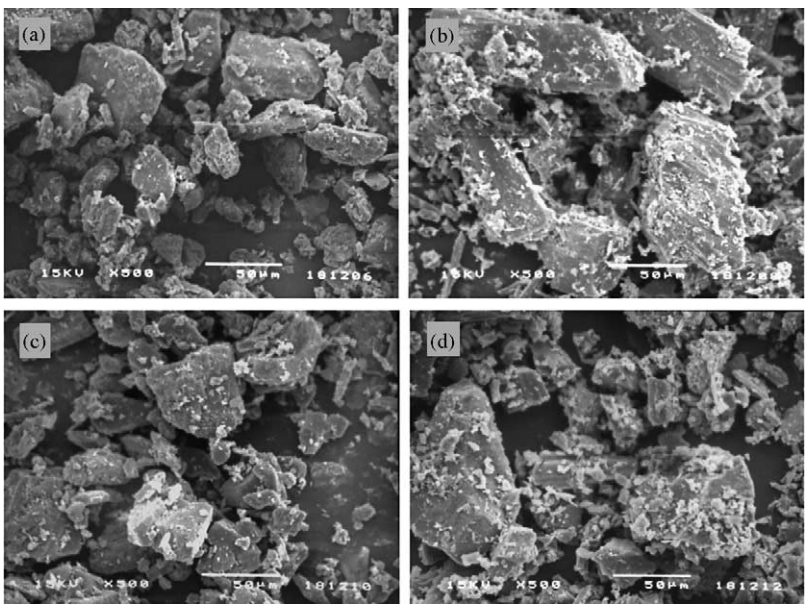

Fig. 4. Scanning electron micrographs of NIF/mannitol physical mixtures (PM) and solid dispersions (SD): (a) PM 10% (w/w) NIF, (b) SD 10% (w/w) NIF, (c) PM 50% (w/w) NIF, (d) SD 50% (w/w) NIF; magnification 500×.

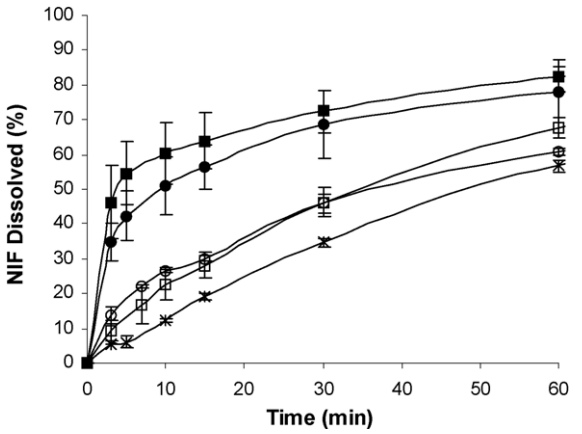

Fig. 5. Dissolution profiles of NIF, NIF/mannitol physical mixtures (PM) and solid dispersions (SD): (□), PM 10% (w/w) NIF; (◯), PM 50% (w/w) NIF; (■), SD 10% (w/w) NIF; (●), SD 50% (w/w) NIF; (×), pure NIF.

particle size reduction, the absence of crystal structure and improved wettability (Leuner and Dressman, 2000). In our case, the information supplied by DSC indicates that there was no amorphous NIF present (Fig. 2), and SEM micrographs demonstrate approximately equal NIF particle size of systems under investigation (Fig. 4). Higher dissolution rate of NIF in solid dispersions was therefore attributed to improved wetting of the crystal surface mainly due to attached mannitol particles, which provoked the solubilizing effect. The carrier attracts the dissolution medium and increases its amount in the immediate vicinity of the NIF surface. Furthermore, the arrangement of carrier physically separates drug particles, preventing their aggregation after introduction of the solid-dispersed system to the dissolution medium (Craig, 2002). The appearance of mannitol in thermodynamically less stable polymorphic modification II could also contribute to enhanced dissolution rate from solid dispersions. However, Burger et al. (2000) reported only a small differences between mannitol modifications I and II (melting points 166.5 and 166 °C, heats of fusion 53.5 and 52.1 kJ/mol, respectively, and resembling crystal lattice with orthorhombic space group).

Table 1
Dissolution properties of nifedipine, physical mixtures and solid dispersions with mannitol

Sample	Mean ± S.D.	
	D_{15} (%)[a]	$t_{50\%}$ (min)[b]
Pure nifedipine	19.1 ± 0.8	50.9 ± 2.1
10% Physical mixture	26.0 ± 1.3	35.3 ± 5.3
10% Solid dispersion	59.9 ± 1.4	5.3 ± 0.7
50% Physical mixture	30.1 ± 1.1	37.7 ± 4.8
50% Solid dispersion	53.4 ± 1.4	11.8 ± 2.6

[a] Amount of nifedipine dissolved after 15 min.
[b] Time when 50% of initial amount of nifedipine was dissolved.

4. Conclusion

The dissolution rate of NIF from solid dispersions with mannitol was markedly increased in comparison to pure NIF and physical mixtures. We assume the main reason for dissolution rate enhancement was improved wetting of NIF crystals owing to attachment of mannitol particles on the surface. All other mechanisms can be excluded, since solid-state characterization did not reveal any change in the NIF crystal structure and the size of the NIF particles was preserved.

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