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# HPMC as a potential enhancer of nimodipine biopharmaceutical properties via ball-milled solid dispersions

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ABSTRACT

The poor solubility of drugs remains one of the most challenging aspects of formulation development. Aiming at improving the biopharmaceutical limitations of the calcium channel blocker nimodipine, the development of solid dispersions is proposed herein. Three different proportions of nimodipine:HPMC were tested and all of them generated amorphous solid dispersions. Improvements of up 318% in the solubility and a 4-fold increase in the dissolution rate of nimodipine were achieved. Stability studies conducted over 90 days in a desiccator indicated that the initial characteristic of the formulations were maintained. However, at 40 °C/75% RH recrystallization was observed for solid dispersions with 70 and 80% of HPMC, whilst the formulation composed of 90% of the carrier remained amorphous. The increase in the stability observed when the HPMC concentration was increased from 70 to 90% in the solid dispersions was attributed to the dilution mechanism.



## 1. Introduction

Together with the permeability, the solubility behavior of an active pharmaceutical ingredient (API) is the limiting step in terms of its oral bioavailability (Leuner & Dressman, 2000), particularly for drugs with low gastrointestinal solubility and high permeability (Vasconcelos, Sarmento, & Costa, 2007). Currently, it is estimated that 70% of the new APIs have poor aqueous solubility (Ku & Dublin, 2010), and unfortunately, around 40% of newly developed drugs are rejected by the pharmaceutical industry due to their deficient biopharmaceutical properties (Svenson, 2009).

Several formulation strategies have been proposed to improve the solubility and dissolution rate of poorly water-soluble APIs and of these the solid dispersion (SD) technique has emerged as a particularly effective approach (Alonzo et al., 2011; Konno, Handa, Alonzo, & Taylor, 2008; Newman, Knipp, & Zografi, 2012; Vasconcelos et al., 2007). This technological tool can be defined as the molecular dispersion of a drug in one or more hydrophilic carriers (Padden et al., 2011; Vasconcelos et al., 2007) and its mechanism involves the reduction of the particle size, the enhancement of the wettability of the API in the carrier, the formation of soluble complexes and the obtainment of an amorphous drug (Craig, 2002; Zhong, Zhu, Luo, & Su, 2013). In SDs, hydrophilic polymers also play an important role inhibiting the crystallization of the API through decreasing its molecular mobility (Bhugra & Pikal, 2008; Yonemochi, Sano, Yoshihashi, & Terada, 2013). In this context, the selection of the ideal carrier is crucial to formulation success (Li et al., 2013).

Hydroxypropylmethyl cellulose (HPMC), Fig. 1A, is a non-ionic and water soluble polymer (Rogers, 2009), a mixed cellulose ether (Leuner & Dressman, 2000), which is of great importance as a carrier in drug release systems, including SDs (Asare-Addo, Levina, Rajabi-Siahboomi, & Nokhodchi, 2011; Colombo, 1993; Leuner & Dressman, 2000; Pham & Lee, 1994). In this regard, HPMC is able to enhance the biopharmaceutical properties of many drugs. Etravirine (Qi et al., 2013), fenofibrate (Kalivoda, Fischbach, & Kleinebudde, 2012), mesalazine (Ugandhar, 2012), tacrolimus (Yoshida et al., 2012), raloxifene hydrochloride (Shim et al., 2013) and resveratrol (Wegiel, Mauer, Edgar, & Taylor, 2013) are some of the most recent examples. Publications in the literature report that HPMC can control the drug release rate due to its swelling and dissolution properties in aqueous solution, which are probably associated with the formation of soluble complexes between the water-soluble polymeric carrier and the poorly-water-soluble drug (Oh et al., 2012).

Nimodipine (NMP), Fig. 1B, is a dihydropyridine calcium channel blocker recommended for patients with subarachnoid hemorrhage

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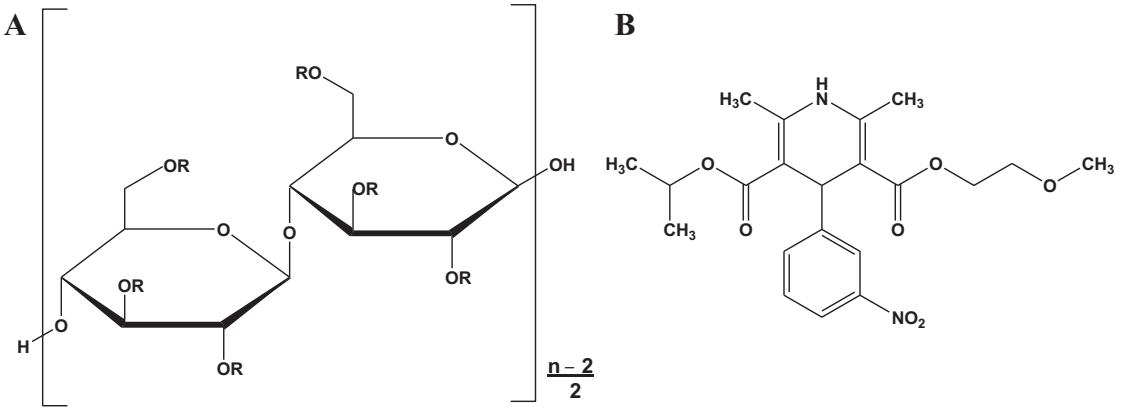


**Fig. 1.** (A) Monomeric unit of HPMC, where R represents either —H, —$CH_3$ or —$CH_2CH(CH_3)OH$; (B) chemical structure of NMP.

(Nguyen, 2004). This compound, which presents low bioavailability (only 13%) and poor solubility in water, belongs to class II in the Biopharmaceutical Classification System (BCS) (Sweetman, 2009), which makes it an ideal candidate for SDs. However, as an aggravating factor, it presents two polymorphs; Modification I (Mod I) or the metastable form, a racemic compound that exhibits higher solubility in water ($360 \pm 70\,\mu g\,L^{-1}$), and Modification II (Mod II), the stable polymorph, which is chemically a conglomerate (Grunenberg, Keil, & Henck, 1995).

Some attempts to improve the biopharmaceutical properties of NMP through SDs obtained via classical techniques have been reported (Adinarayana, Rajendran, & Rao, 2010; Babu, Prasad, & Ramana-Murthy, 2002; Docoslis et al., 2007; Gorajana, Rao, & Nee, 2011; Jijun et al., 2011; Kreidel et al., 2012; Kumar, Kumar, Chanderparkash, & Singh, 2010; Lu, Wang, Ding, & Pan, 1995; Papageorgiou, Docoslis, Georgarakis, & Bikiaris, 2009; Papageorgiou et al., 2006; Smikalla & Urbanetz, 2007; Urbanetz, 2006; Urbanetz & Lippold, 2005; Wu, Zhou, & Zhang, 1998; Yunzhe, Rui, Wenliang, & Tang, 2008; Zheng, Yang, Tang, & Zheng, 2007). The promising results obtained through these studies were determinant in the choice of NMP as a model drug for the obtainment of novel SDs, prepared via an innovative technique and with a potential carrier.

In comparison with other methods used to obtain SDs, high-energy milling has received less attention in the literature (Patterson et al., 2007). However, it can be used to produce amorphous materials (Boldyrev, Shakhtshneider, Burleva, & Severtsev, 1994) or to form regions of drug/excipient miscibility (Friedrich, Nada, & Bodmeier, 2005). During the milling process, sufficient strain is generated in the solid particles through a combination of impact and attrition, producing structural changes on the crystal and the formation of amorphous regions, particularly on the surface (Balani, Ng, Tan, & Chan, 2010; Feng, Rodolfo, & Carvajal, 2008; Mallick et al., 2008). Unlike other techniques, milling is environmentally friendly, since it does not require the use of organic solvents. Also, it consists of a relatively simple process which does not require sophisticated equipment and which generally culminates in a decrease in the total experimental time and easier scaling up (Barzegar-Jalali et al., 2010; Colombo, Grassi, & Grass, 2009; Gaisford, Dennison, Tawfik, & Jones, 2010; Zhong et al., 2013).

In this context, the objective of this study was to verify the potential of using HPMC to obtain amorphous and physically stable ball-milled SDs containing NMP. The aim of preparing these formulations was to improve the biopharmaceutical properties of the API.

## 2. Experimental

### 2.1. Materials

NMP was purchased from Chang Zhow ComWin Fine Chemicals (batch 20110305; Jiangsu, China) and HPMC (Methocel K4 M®) originating from Dow Chemical Company (Midland, USA) was kindly donated by Colorcon do Brasil LTDA (batch TD 100112N11; Cotia, Brazil). High-performance liquid chromatography (HPLC)-grade acetonitrile and methanol were obtained from J.T. Baker (Phillipsburg, NJ). All other chemicals used were pharmaceutical grade. During the analysis, ultrapure water was obtained using a Milli-Q Gradient System (Millipore, Bedford, MA).

### 2.2. Methods

#### 2.2.1. Preparation of ball-milled SDs

Firstly, the drug and carrier were accurately weighed to give a final mass of 2.5 g for all of the formulations prepared. SDs composed of 1:9, 2:8 and 3:7 of NMP:HPMC (w/w) were denoted as 1:9 SD, 2:8 SD and 3:7 SD, respectively. Samples were milled in a Spex Dual Mixer Mill 8000 D (New Jersey, USA) in 40 mL steel jars for 180 min, at a ball:powder ratio of 4:1 (w/w) and with three steel balls (two with an external diameter of 6.4 mm and one of 12.8 mm). Milling was performed at room temperature and no heating of the samples was noted at the end of the process.

#### 2.2.2. Preparation of physical mixtures

Physical mixtures were prepared through simple spatulation of drug and carrier, accurately weighed in different proportions. Samples were denoted as 1:9 PM, 2:8 PM and 3:7 PM, corresponding to NMP:HPMC ratios (w/w) of 1:9, 2:8 and 3:7, respectively.

#### 2.2.3. Stability studies

The samples were stored in a desiccator under vacuum at 40 °C and with 75% of relative humidity (NaCl saturated solution). Solid state stability studies on the SDs of NMP were conducted over a period of 90 days.

#### 2.2.4. HPLC analysis

The LC analysis was performed through a stability-indicating LC-method previously described in the literature (Riekes et al., 2013) and employing a Shimadzu LC-10A system (Kyoto, Japan) equipped with an LC-10AD pump, DGU-14A degasser, SPD-10AV variable-wavelength detector (set at 235 nm) and an SCL-10AVP system controller unit. The experiments were conducted on a

reversed-phase Phenomenex (Torrance, CA) Luna C18 column (250 × 4.6 mm i.d., 5 mm). A security guard holder (C18, 4.0 × 3.0 mm i.d.) was employed to protect the column. The mobile phase was isocratically composed of acetonitrile:methanol:water (55:11:34 v/v/v), with a flow rate of 0.5 mL $min^{-1}$, at 40.0 °C. The samples (at a theoretical concentration of 20 μg $mL^{-1}$) were filtered through a 0.45 mm membrane filter and a volume of 20 μL was injected. Data acquisition was performed using CLASS-VP software to measure the detected peaks. The content of NMP in SDs was expressed as relative values in relation to the theoretical content of the drug in formulations.

*2.2.5. Measurement of solubility*

In order to determine the NMP solubility, an excess of drug in SDs was weighed and added to 30 mL of acetate buffer (pH 4.5) containing 0.3% of sodium lauryl sulfate (SLS), giving a final concentration of 2.0 mg $mL^{-1}$. Samples were kept under stirring at 150 rpm in a thermostatically controlled water bath (37 ± 2 °C) (Dist, model DI-06) until a constant concentration of NMP was reached. At predetermined intervals, aliquots were withdrawn (with immediate replacement of fresh solution) and filtered through 0.22 μm filters before taking the readings on a UV/VIS spectrophotometer (Cary 50 BIO, Varian) at 340 nm.

*2.2.6. Solid-state characterization of ball-milled SDs*

*2.2.6.1. X-ray powder diffraction (XRPD).* X-ray diffraction patterns were obtained using a $\theta$-$\theta$ X-ray diffractometer (Xpert Pro Multi-Purpose Diffractometer, PANAlytical) equipped with Kα copper radiation (λ = 1.5418 Å), operating with a 40 mA current and 45 kV voltage, sample spinner and a Real Time Multiple Strip (RTMS) detector. The measurements were performed at room temperature, scanning at 2θ from 5° to 50°, with a 0.03342° step size and 10.16 s step time.

During the stability studies, the diffractograms were acquired on a $\theta$–$\theta$ X-ray diffractometer (D2 Phaser, Bruker), operating with Kα copper radiation (λ = 1.5418 Å), at a current of 10 mA and voltage of 30 kV. Detection was performed on a scintillation counter one-dimensional LYNXEYE detector. The measurements were taken at room temperature, scanning at 2θ from 5° to 50°, with a 0.091° step size.

*2.2.6.2. Thermal analysis.* Differential scanning calorimetry (DSC) analysis was carried out in triplicate using a Shimadzu calorimeter (DSC-60), operating in a temperature range of 40–130 °C. Samples weighing approximately 2 mg were heated in sealed aluminum crucibles (model 201-53090) and scanned at a first scan mode, at a heating rate of 2 °C $min^{-1}$ and under nitrogen air atmosphere (50 mL $min^{-1}$). The DSC cell was previously calibrated with indium and zinc.

The mass loss of the samples as a function of temperature was determined in triplicate using a Shimadzu thermobalance (TGA-50). Approximately 3 mg of samples were placed in open platinum crucibles which were heated at a heating rate of 20 °C $min^{-1}$, to temperatures ranging from 40 to 800 °C under nitrogen atmosphere (50 mL $min^{-1}$). The instrument was preliminarily calibrated with a standard reference of calcium oxalate.

The thermal data obtained were processed using TA60 software.

*2.2.6.3. Fourier transform infrared (FTIR) spectroscopy.* FTIR spectra were acquired on a Shimadzu spectrophotometer (FTIR Prestige), at room temperature, from 4000 to 400 $cm^{-1}$, with the collection of 20 scans at a resolution of 4 $cm^{-1}$. Samples were prepared by mixing 2% (w/w) of the drug, carrier, physical mixtures and SDs in potassium bromide (KBr).

*2.2.6.4. Scanning electron microscopy (SEM).* The samples were mounted on aluminum stubs, sputtered with gold (IC-50 Ion Coater, Shimadzu, Kyoto, Japan) and analyzed using a scanning electron microscope (SSX-550 Superscan, Shimadzu, Kyoto, Japan) at an accelerating voltage of 10 or 15 kV with different magnifications.

*2.2.7. In vitro dissolution studies*

Dissolution studies of the NMP and SDs were performed using the Varian VK 7000 dissolution device and dissolution apparatus II (paddle), according to the specifications of British Pharmacopeia (British Pharmacopoeia, 2009), which describes the in vitro evaluation of NMP tablets. A known amount of the drug (30 mg) was weighed and submitted to dissolution in 900 mL of previously deaerated acetate buffer (pH 4.5) containing 0.3% of SLS, kept at 37 ± 0.5 °C and rotated at 75 rpm. At predetermined time intervals (5, 10, 15, 20, 25, 30, 45 and 60 min) 4 mL aliquots were withdrawn (with immediate replacement of fresh dissolution medium) and filtered through 0.22 μm filters before readings were taken on a UV/VIS spectrophotometer (Varian UV/VIS CARY) at 340 nm. The correction for the cumulative dilution was calculated. Dissolution experiments were carried out in triplicate and in the absence of light.

Dissolution profiles for the NMP and SDs were compared by independent and dependent methods. For the model-independent analysis, the dissolution efficiency (DE) of the drug and SDs was established. In this analysis the area under the dissolution curve at time $t$ was calculated through the trapezoidal rule and expressed as the percentage of the rectangle area described by 100% of dissolution within the same period. The area under the curve was determined using the Image Tool software, version 3.0. In vitro profiles were also investigated by model-dependent methods, and the data were tested to fit first-order, zero-order, Hixson-Crowell and Higuchi models (O'Hara, Dunne, Butler, & Denave, 1998; Polli, Rekhi, & Shah, 1996). The selection of the model-dependent method was based on the best fit obtained, determined by considering the correlation coefficient (r) most similar to 1. The semi-empirical Korsmeyer–Peppas model was also evaluated correlating drug release to time through a simple exponential equation ($Mt/M\infty = k.t^n$). In this context, $Mt/M\infty$ corresponds to the proportion of drug released at time $t$, $k$ is the kinetic constant, and it has been proposed that the exponent $n$ is indicative of the release mechanism (Korsmeyer, Gurny, Doelker, Buri, & Peppas, 1983).

## 3. Results and discussion

*3.1. HPLC analysis*

The experimental and relative values regarding the contents of NMP in SDs were 100.61 ± 0.43%, 98.98 ± 0.04% and 99.43 ± 0.35% for 1:9 SD, 2:8 SD and 3:7 SD, respectively. Also, no degradation peak was observed in the chromatograms analyzed (Supplementary Fig. A.1), indicating the stability of the drug on employing this technique.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2013.08.046.

*3.2. Measurement of solubility*

The results obtained for the NMP solubility indicated that improvements were achieved for all of the SDs. Increases of 318.80 ± 1.31%, 156.14 ± 1.29% and 102.87 ± 0.99% were observed for 1:9 SD, 2:8 SD and 3:7 SD, respectively. These data indicate that the solubility of NMP in these SDs was dependent on the carrier concentration, the best result being obtained for the formulation in which the proportion of HPMC was 90% with 10% of NMP. Also, the

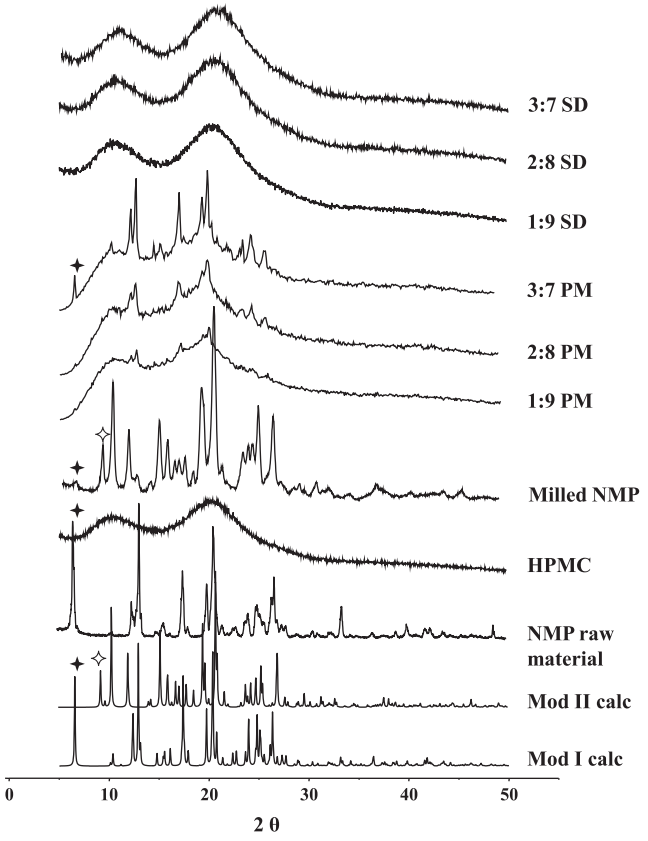


**Fig. 2.** Calculated X-ray patterns of Mod I and Mod II and X-ray diffractograms of raw materials, physical mixtures and SDs. The symbol ✦ indicates the reflection at 6.6°, characteristic of Mod I, whilst ✧ indicates the reflection at 9.3°, which is present exclusively at Mod II.

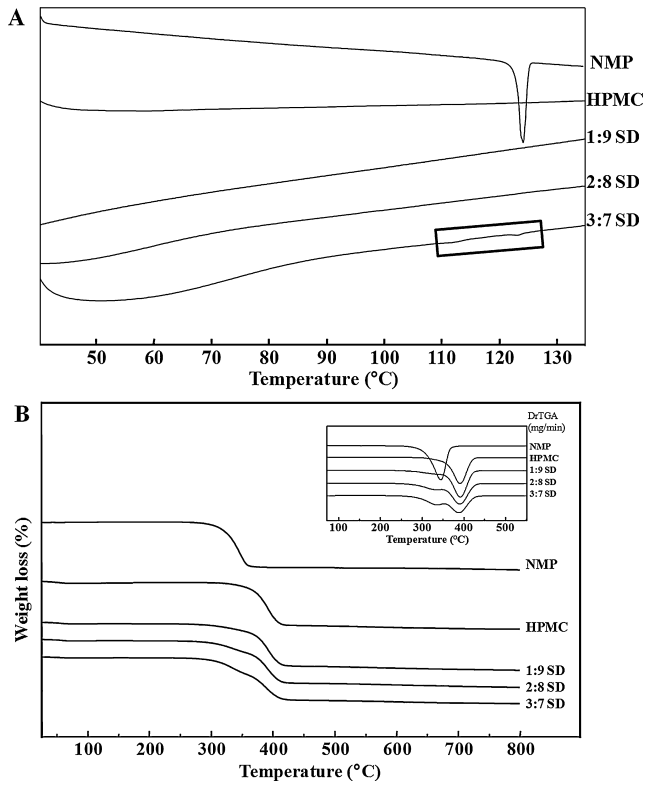


**Fig. 3.** (A) DSC curves and (B) TGA curves of raw materials and SDs. In the upper right corner of (B), derivate thermogravimetric curves (DrTGA) of the samples are presented.

increased solubility of NMP in the presence of HPMC could be due to the formation of soluble complexes between the water-soluble polymeric carrier and poorly soluble drug (Oh et al., 2012).

### 3.3. Solid-state characterization of ball-milled SDs

#### 3.3.1. XRPD

X-ray diffraction patterns related to the NMP crystalline phases (Mod I and Mod II) and the raw material, HPMC, physical mixtures and SDs are shown in Fig. 2.

According to Grunenberg, Keil and Henck, NMP presents two crystalline phases: Modification I (Mod I) or the metastable form, a racemic compound that exhibits a higher solubility in water ($360 \pm 70\ \mu g\ L^{-1}$), and Modification II (Mod II), the stable polymorph, chemically defined as a conglomerate (Grunenberg et al., 1995). These crystalline modifications can be easily distinguished through various solid-state techniques, and the XRPD analysis produced very different diffractograms for these samples, especially at low 2θ angles. The reflection at 6.6° is only observed for Mod I, whilst that at 9.3° is present exclusively for Mod II (Docoslis et al., 2007; Guo et al., 2011; Riekes et al., 2012; Yang, Ke, Zi, Liu, & Yu, 2008). Through these analyses it is possible to affirm that the raw material acquired for the development of the SDs is composed exclusively of the metastable polymorph Mod I.

On the other hand, the carrier is completely amorphous, in agreement with previous data reported in literature (Cilurzo, Minghetti, Casiraghi, & Montanari, 2002; Oh et al., 2012). For all of the physical mixtures, it is possible to observe the crystalline reflections of the drug overlapping the amorphous halo of the polymer. These data indicate the absence of physical interactions between NMP and HPMC and also verify that amorphous halos related to the SDs are due to the preparation process.

In order to determine the drug behavior during milling without a polymeric carrier, NMP was milled for 3 h. It is extremely important to note that without HPMC the API did not become amorphous. In addition, the initial polymorph Mod I underwent a partial solid-state transition to the less soluble crystalline phase Mod II, since both characteristic reflections at 6.6° (Mod I) and at 9.3° (Mod II) were observed for this sample. These data demonstrate the importance of adding HPMC to obtain amorphous SDs containing NMP.

Also, as can be observed, all of the SDs showed amorphous characteristics, explaining the increase in the solubility of NMP in these formulations. The enhanced solubility is the result of the disordered structure of the amorphous solid. Because of the short-range intermolecular interactions in an amorphous system no lattice energy has to be overcome, whereas in the crystalline material the lattice has to be disrupted in order for it to dissolve (Sathigari, Radhakrishnan, Davis, Parsons, & Babu, 2012; Shah, Kakumanu, & Bansal, 2006).

#### 3.3.2. Thermal analysis

The DSC and thermogravimetric curves for the drug, carrier and SDs are shown in Fig. 3. According to Grunenberg, Keil and Henck NMP polymorphs can be also distinguished by means of DSC, since Mod I shows an endothermic event at $124 \pm 1$ °C and Mod II melts at $116 \pm 1$ °C (Grunenberg et al., 1995). As can be observed, the NMP raw material presented a single melting event at 124.1 °C, confirming its identity as pure Mod I. These data are in agreement with the previous XRPD results. No endothermic event was observed for HPMC, which is consistent with data reported in the literature (Asare-Addo et al., 2011). However, discrete endothermic events at 115 and 125 °C were observed for the sample 3:7 SD, indicating a crystallization of NMP into its two polymorphs during the DSC

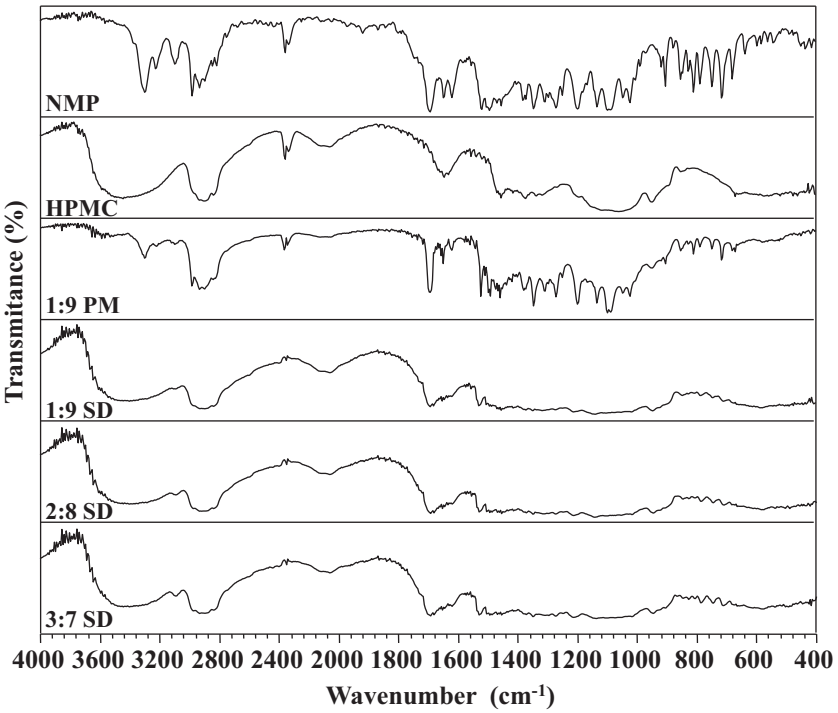


**Fig. 4.** FTIR spectra of raw materials, physical mixture and SDs.

analysis, at elevated temperatures. The absence of crystallization or melting events for the samples 1:9 SD and 2:8 SD, besides indicating their amorphous state, may be due to the lower contents of drug in these samples, which are probably lower than the limits of detection for each polymorph (Riekes et al., 2012). It is very important to mention that the endothermic events found for the sample 3:7 SD does not indicate that this SD is crystalline, since the X-ray analysis verified its amorphous state. In addition, although a single glass transition temperature ($T_g$) was expected to verify the miscibility of the amorphous phases in the obtained SDs (Palermo, Anderson, & Drennen, 2012), none of the DSC curves showed it. This fact can be explained by the very broad $T_g$ of the heterogeneous HPMC.

The thermogravimetric analysis revealed that the NMP was thermally stable up to approximately 250 °C, presenting a single weight loss event (96.2%) in the temperature range analyzed. The thermal degradation peak, obtained through derivative thermogravimetry, occurred at 347.2 °C. These data are in agreement with previous reports in the literature (Cardoso, Rodrigues, Stulzer, Silva, & Matos, 2005). A higher thermal stability was noted for HPMC, also in a single stage of degradation. The thermal degradation occurs at between 335 °C and 425 °C, with a peak temperature of 391 °C. The weight loss for HPMC was of 93.4%. For the SDs the thermal degradation occurred in two steps (as evidenced by the DrTGA curves), and the relative proportion of the two degradation events is directly proportional to the NMP and HPMC contents of the samples. The first event represents the presence of NMP, whilst the second one is related to HPMC. The weight losses were 94.2%, 93.7% and 92.3%, for 1:9 SD, 2:8 SD and 3:7 SD, respectively.

### 3.3.3. FTIR spectroscopy

The FTIR spectra for NMP, HPMC, 1:9 PM and SDs are shown in Fig. 4.

Characteristic bands for NMP appear at 3293 $cm^{-1}$, related to N—H stretching of the polymorph Mod I, at 1695 $cm^{-1}$, associated with the carbonyl bond, and at 1523 $cm^{-1}$, representing the $NO_2$ group (Barmpalexis, Kachrimanis, & Georgarakis, 2011; Hu et al., 2003; Papadimitriou, Papageorgiou, Kanaze, Georgarakis, & Bikiaris, 2009; Tang, Pikal, & Taylor, 2002). In the case of HPMC, bands were observed at 3443 $cm^{-1}$ (O-H stretching), at 2935 $cm^{-1}$ (C—H stretching), at 1651 $cm^{-1}$ (C═O of the glucose unit) and at 1069 $cm^{-1}$ (C—O—C group) (Anuar, Wui, Ghodgaonkar, & Taib, 2007; Oliveira, Bernardi, Murakami, Mendes, & Silva, 2009). In the physical mixture, all of the characteristic bands for the drug and carrier are overlapped, indicating the absence of physical interactions between these compounds. On the other hand, bands related to the amine group of NMP disappeared for all of SDs, confirming the amorphous characteristic of these formulations (Barmpalexis et al., 2011), as previously observed through XRPD and DSC analysis. Also, although shifts for the bands related to HPMC were not observed, the merging of the O—H band of the carrier with the N—H band of NMP indicates the establishment of hydrogen bonding in SDs. It is important to mention that this kind of interaction between drug and carrier is an additional benefit for the SDs, since they can increase the solid solubility of the drug into the hydrophilic carrier besides acting on inhibiting the crystallization of the drug from a glass solution (Marsac, Shamblin, & Taylor, 2006; Van den Mooter, 2012). Cilurzo, Minghetti, Casiraghi and Montanari also observed the disappearance of N—H stretching vibrations for amorphous SDs composed of nifedipine and HPMC (Cilurzo et al., 2002).

### 3.3.4. SEM

Photomicrographs of the drug, carrier and SDs are shown in Supplementary Fig. A.2. Small tabular crystals with a homogeneous particle size distribution can be observed for the NMP raw material. However, particles with undefined shapes are observed for HPMC. From these images it can be verified that the milling promoted considerable changes in the morphology of the NMP and HPMC, generating agglomerates which did not seem to be influenced by the drug:carrier proportion. It is important to mention that crystals of the drug were not observed on the surface of the formulations, confirming its amorphous characteristic in SDs. Also, as no decrease in particle size was noted for 1:9 SD, 2:8 SD and 3:7 SD, it is assumed that the enhancement in NMP solubility is due to the amorphous

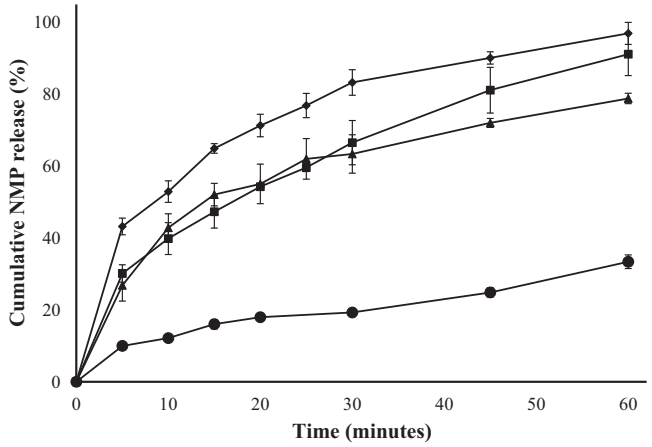


**Fig. 5.** Release rates of (♦) 1;9 SD, (■) 2:8 SD, (▲) 3:7 SD and (●) pure NMP in acetate buffer pH 4.5 containing 0.3% of SLS.

characteristic, the establishment of hydrogen bonding and the presence of a hydrophilic carrier in SDs, which probably improved the wettability of these formulations.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2013.08.046.

### 3.4. In vitro dissolution studies

The release rates of the different SDs of NMP in acetate buffer (pH 4.5) containing 0.3% of SLS and of the pure drug are compared in Fig. 5.

As can be observed, all of the SDs were able to increase the dissolution rate of NMP. These data are in agreement with the enhancement of the drug solubility in these formulations. The formulation 1:9 SD promoted the release of approximately 100% of NMP in 60 min, which indicates a 3-fold increase in the drug dissolution during this period. Also, 2:8 SD and 3:7 SD presented very similar release profiles for up to 30 min, after which 2:8 SD demonstrated a higher dissolution rate. According to Kogermann et al. (2013), this deviation in the dissolution behaviors in the later stages of a dissolution testing could be associated with the formation of physically different diffusion layers around the drug:polymer particles, since it is well known that the dissolution of the drug follows the dissolution of the polymer. The values for the percentage drug release of these SDs were 91.2 ± 5.9% (2:8 SD) and 78.8 ± 1.4% (3:7 SD) at the end of the assay. These results indicate that the improvement of this biopharmaceutical property was dependent on the drug:carrier ratio, the best results being obtained for the SD with the highest proportion of HPMC.

It is also important to mention that the dissolution data for 1:9 SD, 2:8 SD and 3:7 SD were within the acceptance criteria of deviation required by the United States Pharmacopoeia. This means that the relative standard deviation (RSD) values at time intervals of 10 min or less were lower than 20%, and for longer intervals they were lower than 10%. The fulfillment of this condition is essential, since a high variability in the results can hinder the identification of trends or effects resulting from changes in the formulation (USP, 2011). Also, achieving the desired deviation range is even more challenging for HPMC-based formulations, since HPMC is known to form hydrogels which slowly erode in aqueous solutions and can result in variability among samples (Kim et al., 2006).

Data related to the analysis of the dissolution profiles through independent and dependent methods are shown in Table 1.

Regarding the dissolution efficiency (DE), SDs increased this value considerably, since for the pure drug the DE was 19.4 ± 0.6%.

**Table 1**
Dissolution efficiency (DE), period in which 50% release of NMP occurs ($t_{50\%}$) and dissolution rate constant ($k$) for SDs.

| Sample | DE (%) ± standard deviation | $t_{50\%}$ (min) | $k$ (min$^{-1}$) |
|---|---|---|---|
| 1:9 SD | 71.5 ± 0.9 | 242.73 | 16.00 |
| 2:8 SD | 59.0 ± 3.6 | 246.23 | 12.88 |
| 3:7 SD | 58.8 ± 3.7 | 318.88 | 12.09 |

Increases in this parameter by up to a factor of four were noted for the formulations obtained in comparison to NMP. The release profiles were also tested through different mathematical models and the best fit was observed for the Higuchi model. According to this model, when exposed to the solvent, both the drug and carrier dissolve at rates proportional to their solubility and diffusion coefficients in the dissolving medium. In this context, the dissolution rate of the minor component may be determined by the component in excess. In turn, this may be applied to solid dispersal systems by arguing that when the drug is present as a minority component its dissolution will be dominated by the dissolution behavior of the carrier (Corrigan, 1986; Craig, 2002; Higuchi, 1967; Higuchi, Mir, & Desai, 1965).The Korsmeyer–Peppas model correlates the drug release to time through a simple exponential equation for a drug release fraction of <0.6. This model has been used to evaluate the drug release from polymeric devices, especially when the release mechanism is unknown or when there is more than one mechanism involved (Korsmeyer et al., 1983). In this context, $n \leq 0.43$ indicates Fickian release and $n = 0.85$ indicates a purely relaxation-controlled delivery which is referred to as Case II transport. Intermediate values ($0.43 < n < 0.85$) indicate an anomalous behavior, described as a non-Fickian kinetics corresponding to coupled diffusion and polymer relaxation. Occasionally, values of $n > 1$ have been observed which are regarded as Super Case II kinetics (Ritger & Peppas, 1987, 1987a).The results obtained through the application of the Korsmeyer–Peppas model show calculated $n$ values of 2.92, 2.2 and 2.3, for 1:9 SD, 2:8 SD and 3:7 SD, respectively, indicating that the NMP was released via Super Case II transport. In the case of this mechanism, it is proposed that the drug release involves diffusion,

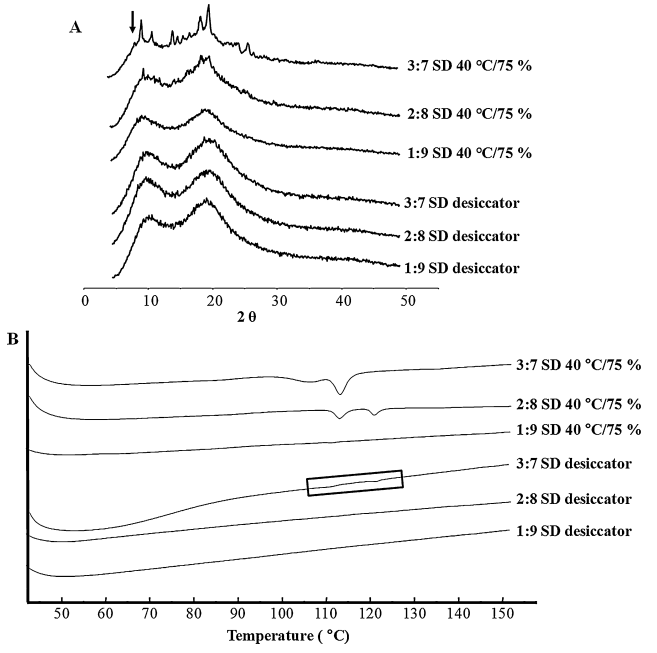


**Fig. 6.** (A) XRPD patterns and (B) DSC curves of SDs after 90 days of stability studies at different conditions. The arrow at the X-ray pattern of 3:7 SD indicates the reflection at 9.3°, characteristic of Mod II.

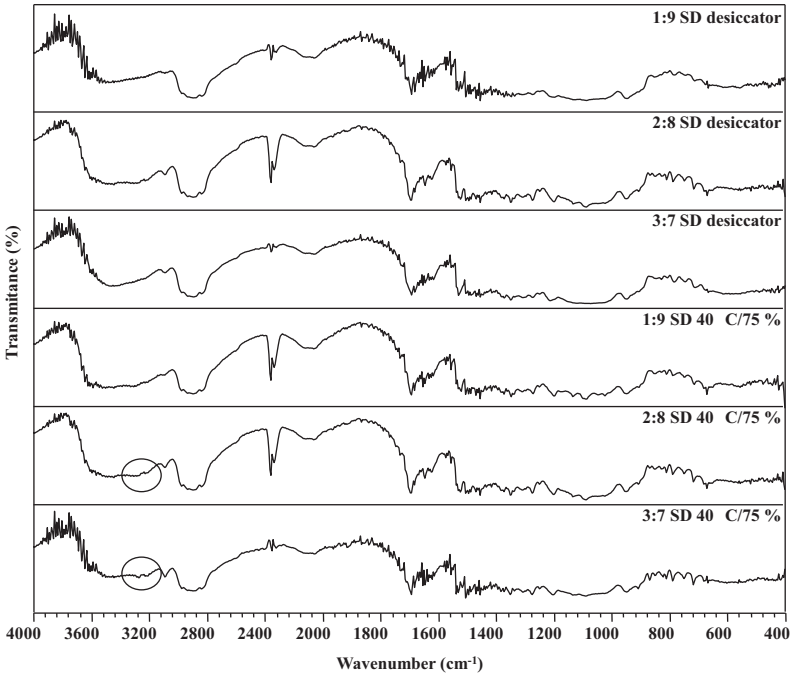


**Fig. 7.** FTIR spectra of SDs kept 90 days at different conditions. The highlighted areas show the appearance of the amine group bands respective to crystalline NMP.

swelling, relaxation and erosion (Ritger & Peppas, 1987a) of the polymeric component.

### 3.5. Stability studies

Stability studies on the physical state of the SDs were performed through XRPD, DSC and FTIR spectroscopy. The data obtained are shown in Figs. 6 and 7.

As can be observed through XRPD data, all of the SDs remained amorphous for 90 days in a desiccator. No changes were observed in the FTIR spectra, indicating the maintenance of the initial interactions between the drug and carrier. These data suggest that the formulations remained stable under this condition. Also, the crystallization of the sample 3:7 SD during the DSC analysis was still observed and its cause was already discussed in Section 3.3.2.

On the other hand, distinct results were obtained when the samples were submitted to more severe conditions of temperature and humidity. At 40 °C/75% RH, only the sample 1:9 SD remained amorphous, as indicated by the XRPD, DSC and FTIR spectroscopy data. The X-ray diffractograms for 2:8 SD and 3:7 SD clearly indicated the recrystallization of these samples, and the characteristic reflection of Mod II, at 9.3°, was observed for the formulation 3:7 SD. These data were confirmed by the DSC results and the thermal analysis also revealed the polymorphic mixture of 2:8 SD. The spectroscopy analysis shows the appearance of amine group bands related to crystalline NMP at 3269 $cm^{-1}$ for the samples 2:8 SD and 3:7 SD, indicating the presence of the crystalline phase Mod II (Barmpalexis et al., 2011; Tang et al., 2002).

Reports in the literature indicate that exposure to high humidity leads to a greater absorption of moisture by the bulk structure of SDs, in addition to surface adsorption, compared to physical mixtures of similar composition. This absorbed water content can induce plasticization and enhance molecular mobility, thereby leading to crystallization (Ahlneck & Zografi, 1990; Sakurai, Sako, & Maitani, 2012; Takeuchi, Yasuji, Yamamoto, & Kawashima, 2000).

It is well known that thermodynamically unstable systems, like amorphous systems, tend to undergo recystallization to their more stable state at any given moment (Serajuddin, 1999). However, various studies have demonstrated that the presence of hydrophilic carriers inhibits the recrystallization of amorphous drugs (Bhugra & Pikal, 2008; Bikiaris, 2011; Leuner & Dressman, 2000; Newman et al., 2012; Sethia & Squillante, 2003; Van den Mooter, 2012). This inhibition is generally attributed to the interaction between drug and carrier, promoted mainly through hydrogen bonds, and to the dispersion of drug molecules in the polymeric matrix during the preparation process (Leuner & Dressman, 2000). In the case of SDs of NMP, the increase in the stability observed when the HPMC concentration was increased from 70 to 90% (w/w) was attributed to the dilution mechanism, where the drug was diluted in the polymer and the diffusion pathway for crystallization increased, thereby slowing the process (Bhugra & Pikal, 2008; Konno & Taylor, 2006).

## 4. Conclusions

SDs composed of NMP and HPMC, in different proportions, were successfully obtained through ball milling and achieved the desired aims. All of the solid-state techniques demonstrated that 1:9 SD, 2:8 SD and 3:7 SD were amorphous and FTIR data verified the establishment of hydrogen bonding between drug and carrier. The enhancement of the biopharmaceutical properties of the API was achieved for all formulations, although the best results were attributed to the sample 1:9 SD. This SD was able to improve the drug solubility by up 318% and the NMP dissolution rate by up to a factor four. In addition to promoting the best performance in terms of these properties, a higher proportion of HPMC in the formulations led to a greater stability of the SDs at 40 °C/75% RH, due to a dilution mechanism. No changes were noted for the SDs over 90 days of storage in a desiccator, with respect to the physical characteristics. These results verify the potential of HPMC as a polymeric carrier for ball-milled SDs of NMP and highlight the future perspectives for these systems, especially for the sample 1:9 SD, which include the obtainment of solid dosage forms and the determination of their bioavailability compared with commercial formulations.

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