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Physical properties and solubility studies of Nifedipine-PEG 1450/HPMCAS-HF solid dispersions

Abstract

Low-order high-energy nifedipine (NIF) solid dispersions (SDs) were generated by melt solvent amorphization with polyethylene glycol (PEG) 1450 and hypromellose acetate succinate (HPMCAS-HF) to increase NIF solubility while achieving acceptable physical stability. HPMCAS-HF was used as a crystallization inhibitor. Individual formulation components, their physical mixtures (PMs), and SDs were characterized by differential scanning calorimetry, powder X-ray diffraction, and Fourier transform infrared spectroscopy (FTIR). NIF solubility and percent crystallinity (PC) were determined at the initial time and after 5 days stored at 25 °C and 60% RH. FTIR indicated that hydrogen bonding was involved with the amorphization process. FTIR showed that NIF:HPMCAS-HF intermolecular interactions were weaker than NIF:PEG 1450 interactions. NIF:PEG 1450 SD solubilities were significantly higher than their PM counterparts ($p < 0.0001$). The solubilities of NIF:PEG 1450:HPMCAS-HF SDs were significantly higher than their corresponding NIF:PEG 1450 SDs ($p < 0.0001$ -0.043). All the SD solubilities showed a statistically significant decrease ($p < 0.0001$) after storage for 5 days. SDs PC were statistically lower than their comparable PMs ($p < 0.0001$). The PCs of SDs with HPMCAS-HF were significantly lower than SDs not containing only PEG 1450. All SDs exhibited a significant increase in PC ($p < 0.0001$ -0.0089) on storage. Thermogravimetric analysis results showed that HPMCAS-HF bound water at higher temperatures than PEG 1450 ($p < 0.0001$ -0.0039). HPMCAS-HF slowed the crystallization process of SDs, although it did not completely inhibit NIF crystal growth.

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Comments

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Physical Properties and Solubility Studies of Nifedipine-PEG 1450/HPMCAS-HF Solid Dispersions

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Graphical Abstract

Abstract

Low-order high-energy nifedipine (NIF) solid dispersions (SDs) were generated by melt solvent amorphization with PEG 1450 and HPMCAS-HF to increase NIF solubility while achieving acceptable physical stability. HPMCAS-HF was used as a crystallization inhibitor. Individual formulation components, their physical mixtures (PMs), and SDs were characterized by DSC, PXRD, and FTIR. NIF solubility and percent crystallinity (PC) were determined at initial time and after 5 days stored at 25 °C and 60% RH. FTIR indicated that hydrogen bonding was involved with the amorphization process. FTIR showed that NIF:HPMCAS-HF intermolecular interactions were weaker than NIF:PEG 1450 interactions. NIF:PEG 1450 SD solubilities were significantly higher than their PM counterparts ($p < 0.0001$). The solubilities of NIF:PEG 1450:HPMCAS-HF SDs were significantly higher than their corresponding NIF:PEG 1450 SDs ($p < 0.0001-0.043$). All the SD solubilities showed a statistically significant decrease ($p < 0.0001$) after storage for five days. SDs PC were statistically lower than their comparable PMs ($p < 0.0001$). The PCs of SDs with HPMCAS-HF were significantly lower than SDs not containing only PEG 1450. All SDs exhibited a significant increase in PC ($p < 0.0001-0.0089$) on storage. TGA results showed that HPMCAS-HF bound water at higher temperatures than PEG 1450 ($p < 0.0001-0.0039$). HPMCAS-HF slowed the crystallization process of SDs, although it did not completely inhibit NIF crystal growth.

Key words

Amorphization, DSC, FTIR, PXRD, melt solvent method, nifedipine, PEG 1450, HPMCAS-HF, solid dispersions, solubility

1. Introduction

Combinatorial chemistry and high throughput screening approaches have been widely used in the last two decades to identify potential new drug candidates. The majority of these candidates are either weak acids (a) or weak bases (b). In the expanded Biopharmaceutical Classification System (BCS), many of these candidates are identified as Class IIa and Class IIb compounds that have low solubility and high permeability (Tsume et al. 2014). A limited solubility of these Class II drugs impedes the oral bioavailability, and presents a key challenge in the development of novel drug candidates. Thus, the use of innovative technologies to improve drug solubility and dissolution rate has become an important product development strategy.

Drug amorphization is a promising approach to improve the solubility and subsequent oral bioavailability of Class IIa and Class IIb drug candidates (Kesisoglou et al. 2007; Vasconcelos et al. 2007; Tsume et al. 2014). A solid dispersion (SD) is an important amorphization technique used to improve the drug solubility (Serajuddin 1999). Amorphous and low-ordered drug materials are higher energetic forms than their crystalline counterparts, which results in a higher apparent drug dissolution and solubility. These higher energy forms are also chemically and physically less stable than their crystalline counterparts. When drug amorphization technologies are used to increase drug solubility, the overarching product design goal is to create a higher energetic dosage form while ensuring product stability throughout its shelf life. Typically, amorphization is accomplished using a drug-polymer carrier system. These low-order materials exhibit greater molecular mobility. This increased mobility can accelerate the nucleation and crystallization process. Moisture present in the SD can also increase molecular mobility and support the drug nucleation process.

Weakly acidic nifedipine (NIF) was chosen as a model Class IIa compound (Fig. 1) for amorphization studies. The aim of this investigation was to improve NIF's solubility while minimizing drug re-crystallization. NIF SDs were prepared using polyethylene glycol (PEG) 1450 with and without hypromellose acetate succinate (HPMCAS-HF). The working hypothesis states that intermolecular hydrogen bonding interactions between NIF and PEG 1450 in the presence of HPMCAS-HF would provide enhanced solubility and minimize recrystallization compared to a NIF:PEG 1450 SD alone. Kestuer and Taylor reported that strong and extensive hydrogen bonding between felodipine and povidone led to an effective inhibition of drug

crystallization in the SDs (Kestur and Taylor 2010). PEG 1450 was also expected to function as a cosolvent in the dissolution media to enhance NIF solubility. HPMCAS-HF was chosen as a functional excipient to maintain solubility enhancement, and as a crystallization inhibitor (Tanno et al. 2004; Ueda et al. 2013). HPMCAS-HF is known to intercalate with the molecules by hydrogen bonding to inhibit the crystallization (Konno Hajime and Taylor Lynne S. 2008).

SDs are generally prepared by melt or solvent evaporation methods. In this study, a melt solvent method was used to prepare the dispersions. The drug-polymer physical mixtures (PMs) and their SDs were studied by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction (PXRD), and Fourier transform infrared spectroscopy (FTIR). The drug-polymer dispersions and PMs were stored at controlled conditions (25 ± 2 °C / $60 \pm 5\%$ RH) to study the re-crystallization tendency of the NIF:PEG 1450 and NIF:PEG 1450:HPMCAS-HF dispersions.

2. Materials and methods

NIF (Lot no: YT4QE-OC) was purchased from Tokyo Chemical Industry, Tokyo, Japan. NIF reference standard (Lot no.: MKBR1676V) and PEG 1450 (Lot no.: 122K0094) were bought from Sigma Aldrich, St. Louis, MO. HPMCAS-AF (Lot no.: 4103177) was obtained as a gift from Shin-Etsu Chemical Co. Ltd., Tokyo, Japan.

2.1. Solubility measurement of NIF

Approximately 10.00 mg NIF was dissolved in 20 mL of deionized water in a closed flat-bottomed vial covered with aluminum foil. This solution was subjected to continuous stirring for three days at room temperature. The solution was filtered using a Acrodisc® 0.45 μ , 13 mm nylon membrane syringe filter (PALL Life Sciences, Exton, PA). The NIF concentration in the filtrate was analyzed by high performance liquid chromatography (HPLC). Filter absorption studies were performed. It was determined that 10 mL of filtrate provided a constant NIF concentration. The amount of NIF placed in each vial was in excess of its reported solubility value of 5.6 mg/L (Ali and Florey 1989). All analyses were performed in triplicate.

2.2. HPLC measurements

Reverse phase HPLC was used to quantify the NIF concentration in solutions. Precision, accuracy, selectivity, linearity, and ruggedness were determined by the United States

Pharmacopeia (USP) 40-NF 35 methods (USP 2017). HPLC studies were carried out with an Agilent 1100 series system (Agilent Technologies, Santa Clara, CA). A Luna C₁₈ 5 μ packing 150 x 4.6 mm column (Phenomenex, Torrance, CA) at 40 °C and NIF reference standard were used for analysis. NIF was detected at a wavelength of 236 nm using a UV photodiode array detector. The mobile phase was composed of acetonitrile and water in 2:1 v/v. The isocratic elution method used a 10.00 μ L injection volume, 0.7 mL/min flow rate, and 6 min run time. The elution time was 3.5 min. A freshly prepared mobile phase was pumped through the UV-HPLC system for 20-30 min prior to each run until a stable baseline was achieved.

2.3. Preparation of PMs

Five grams of NIF:PEG 1450 PMs were prepared in ratios of 1:2, 1:4, 1:8, and 1:10 w/w. Accurately weighed NIF and PEG 1450 were blended thoroughly via geometric mixing. These PMs were stored in amber colored vials.

2.4. Preparation of NIF SDs

The SD terminology used throughout the remainder of this research report is described here. NIF:PEG 1450 and NIF:PEG 1450:HPMCAS-HF indicates the individual components of the SD. In the case where it is important to note the specific NIF and PEG 1450 ratios in the SDs (without HPMCAS), the SD's nomenclature will use NIF:PEG 1450 (specific ratio). To indicate the specific ratio of NIF and PEG 1450 for SDs of NIF, PEG 1450 and HPMCAS-HF, the nomenclature will be NIF:PEG 1450 (specific ratio):HPMCAS-HF.

NIF:PEG 1450 SDs were prepared in ratios of 1:2, 1:4, 1:8, and 1:10 w/w with and without HPMCAS-HF by the melt solvent method (Vo et al. 2013). A designated amount of PEG 1450 was weighed in a glass beaker which was heated to 60 °C to melt the polymer. Acetone was used to dissolve NIF and HPMCAS-HF. In the case of NIF:PEG 1450 SD, NIF was dissolved in 150 mL of acetone and was added to previously molten PEG 1450 polymer. The resulting solution was mixed at room temperature for 10 min with magnetic stirrer. This solution was transferred to a round bottom flask and connected to a rotary evaporator set at 150 bar. The temperature of the circulating chiller was set at 0 °C and the water bath was set at 30 °C. The flask was rotated at 30 rpm and vacuum dried for 15 min. SDs of NIF and PEG 1450 containing 25% w/w HPMCAS-HF were prepared using the same procedure. Both NIF and HPMCAS-HF were dissolved in 300 mL of acetone. This solution was then added with stirring to the molten PEG 1450.

2.5. Characterization of NIF, PEG 1450, HPMCAS-HF, their PMs, and SDs

Individual formulation components (NIF, PEG 1450, and HPMCAS-HF), their PMs, and SDs were characterized by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction (PXRD), and Fourier transform infrared spectroscopy (FTIR).

2.5.1. DSC/TGA

Open pan DSC measurements of NIF, PEG 1450, HPMCAS-HF and their PMs were performed using a calibrated DSC Q200 (TA instrument, New Castle, DE). Approximately 3 g of sample were weighed into an aluminum pan. The samples were heated from a temperature of 20 °C to 250 °C with an increase of 10 °C/min. The DSC transitions are reported as peak temperatures. TGA was carried out using a calibrated TGA Q500 (TA instrument, New Castle, DE). Approximately 6 g of sample was weighed into a platinum pan. Samples were heated at a heating rate of 10 °C/min from 20 °C to 250 °C, depending on the sample material. Nitrogen was purged at a flow rate of 40 mL/min for both DSC and TGA. Data was analyzed by using Universal Analysis Software[®] Version 4.5A (TA instrument, New Castle, DE). All experiments were performed in triplicate.

2.5.2. PXRD

The PXRD studies were performed using a Rigaku Ultima-IV X-ray powder diffractometer (Rigaku Americans, The Woodlands, TX). This diffractometer was equipped with a Bragg-Brentano geometry ($\theta/2\theta$). A scintillation counter was used to monitor the X-ray diffraction. Monochromatic CuK β radiation ($\lambda = 1.5406 \text{ \AA}$) was used at an operating voltage and amperage of 40 mV and 44 mA, respectively. Samples were mounted evenly as a thin layer on a glass slide. Samples were scanned from 5° to 40° 2θ at a rate of 2.00° 2θ /minute. All experiments were performed in triplicate.

2.5.3. Percent crystallinity (PC)

The PXRD patterns were used to calculate PC. Peaks having full-width-at-half-maximum (FWHM) of $< 5^\circ 2\theta$ were considered crystalline in nature. Peaks having FWHM $> 5^\circ 2\theta$ exhibit low molecular order regions. The percentage crystallinity was estimated from Equation 1 (Nunes et al. 2005; Shah et al. 2006).

$$\text{Crystallinity (\%)} = \frac{100A_c}{A_c + A_a} \quad (1)$$

Where, A_c and A_a represents the respective area contributions from the high and low-order crystalline phases. A_a also includes amorphous material. The total area underneath the X-ray peaks ($A_c + A_a$) was calculated between 5° to 40° 2θ using the PDXL software version 1.8.03 (Rigaku Americans, The Woodlands, TX).

2.5.4 FTIR

Test material and potassium bromide (KBr) were accurately weighted in the ratio of 1:100 and mixed thoroughly in a clean mortar and pestle. This mixture was placed in a KBr pellet die and compressed into a transparent pellet. A background scan was performed to remove carbon dioxide and water interference from the spectra. A prepared KBr pellet containing sample was placed in a sample holder. The spectra was collected using an FTIR spectrophotometer (Spectrum One; PerkinElmer®, Waltham, MA) between 4000 to 400 cm^{-1} with a resolution of 4 cm^{-1} . Each individual spectrum was an average of four scans. All experiments were performed in triplicate.

2.5.5 Preliminary physical stability studies

Preliminary physical stability studies were conducted by storing NIF, PEG 1450, their PMs, and SDs with and without HPMCAS-HF in amber colored bottles at controlled temperature and humidity conditions. Samples were stored at controlled conditions ($25 \pm 2^\circ\text{C}$ / $60 \pm 5\%$ RH) for 5 days. Both solubility and PC were analyzed before and after exposure as mentioned in Sections 3.1 and 3.5 respectively. Additionally, percent weight loss associated with unexposed SDs were measured using TGA thermograms. A first derivative of weight change and temperature was used to identify the temperature associated with the maximum rate of water loss in the TGA thermograms of SDs.

2.5.6 Data analysis

The differences between solubility and PC associated with NIF:PEG 1450 PMs, NIF:PEG SDs and, NIF:PEG 1450:HPMCAS-HF SDs were evaluated using JMP® Pro 12.2.0 (SAS Institute, Cary, NC). Sample means were compared by Student's *t*-test, or one-way analysis of variance (ANOVA) followed by Tukey's Honestly Significant Difference (HSD) post-hoc test, wherever applicable. Welch's ANOVA was used when variances of samples were different during

Student's *t*-test analysis. A *p*-value of less than 0.05 was considered significant. The details of statistical interpretation can be found in our previous publication (Gupte et al. 2017).

3. Results and Discussion

3.1. Characterization of NIF and SD components

NIF solubility in water was determined to be 5.52 ± 0.02 $\mu\text{g/mL}$ (Table 1). This solubility value is in agreement with the reported literature (Boje et al. 1988; Ali and Florey 1989). Since NIF exhibited poor aqueous solubility, NIF SDs were prepared using PEG 1450 in the presence and absence of HPMCAS-HF, to study the effect on solubility and physical stability of NIF. NIF PMs and SDs solubilities are discussed in Section 3.5.

Other molecular level properties of drug and SD components were studied using DSC, TGA, PXRD, and FTIR.

Drug and SD component DSC thermograms are provide in Fig. 2a. NIF showed a single sharp melting endotherm at 173.49 ± 0.62 $^{\circ}\text{C}$ compared to the reported value of 171 $^{\circ}\text{C}$ (Friedrich et al. 2005). PEG 1450 melted at 50.34 ± 0.39 $^{\circ}\text{C}$. This is in accordance with the reported 50.8 $^{\circ}\text{C}$ (Frydrych et al. 2015). The NIF melting endotherm was accompanied by weight loss in the TGA thermogram (Fig. 2b), which is most likely due to degradation of NIF upon melting. The PEG 1450 TGA exhibited two plateau regions. Approximately 0.4% weight loss was recorded from 25 to 50 $^{\circ}\text{C}$ and additional 0.3% weight loss from 50 to 110 $^{\circ}\text{C}$. The total weight loss is ascribed to surface moisture. The HPMCAS-HF DSC thermogram exhibited a broad endotherm around 30.86 $^{\circ}\text{C}$. This endotherm was accompanied by a weight loss in the corresponding TGA. The second broad endotherm from 115 to 155 $^{\circ}\text{C}$ is most likely due to a complex set of thermal reactions involving HPMCAS-HF's glass transition temperature at 133 $^{\circ}\text{C}$ (Stroyer et al., 2006) and enthalpic relaxation. The third broad endothermic peak starting around 215 $^{\circ}\text{C}$ was accompanied by TGA weight loss. This weight loss is attributed to the thermal degradation of HPMCAS-HF.

A NIF PXRD (Fig. 3a) exhibited intense sharp peaks at 8.2° , 10.5° , 11.7° , 16.2° , 24.7° , and 26° 2θ (Grooff et al. 2007). PEG 1450 (Fig. 3a) revealed two distinct peaks at 19° and 23° 2θ (Bley et al. 2010). This confirmed the characteristic crystalline nature of NIF and PEG 1450. It is also noted that PEG 1450 has several broad low intensity peaks at ~ 14 - 15° , 26 - 27° , and 35 - 37° 2θ

which have FWHM $>5^\circ 2\theta$ suggesting a low molecular order region. The HPMCAS-HF PXRD (Fig. 3c) showed a characteristic halo pattern indicating its amorphous nature.

The N–H group of pure NIF FTIR spectra (Fig. 4aI) display a stretching vibrations at 3332 cm^{-1} . In the crystalline state, the N–H group of one NIF molecule forms a hydrogen bond with the C=O group of another NIF molecule (Zajc et al. 2005). The stretching vibrations at 3332 cm^{-1} indicate the crystalline nature of NIF and are sensitive to NIF–NIF intermolecular interactions (Iqbal and Chan 2015). NIF–NIF intermolecular hydrogen bonding is further indicated by the presence of strong stretching vibrations at 1679 cm^{-1} and 1689 cm^{-1} that are also sensitive to intermolecular interactions (Cilurzo et al. 2008). PEG 1450 exhibited –OH and C–H stretching vibrations at 3433 cm^{-1} and 2889 cm^{-1} , respectively. In addition, it showed C–H bending vibrations at 1467 cm^{-1} , C–O–C (ether) stretching vibrations at 1280 cm^{-1} , and C–C (ethyl) stretching vibrations at 946 cm^{-1} (Frydrych et al. 2015). The HPMCAS-HF displayed several characteristic stretching vibrations of –OH at 3488 cm^{-1} , –COCH₃ at 1742 cm^{-1} , and C=O at 1121 cm^{-1} . Also, it showed –OR₁R₂ vibrations at 1057 cm^{-1} and 1239 cm^{-1} . These multiple regions serve as a hydrogen bond acceptor sites in HPMCAS-HF (Konno and Taylor 2006; Kothari Khushboo et al. 2015).

3.2. Characterization of PMs of NIF and PEG 1450

A representative DSC thermogram (Fig. 2a) of NIF: PEG 1450 (1:2) PM showed a sharp melting endotherm at $50.69 \pm 0.62^\circ\text{C}$ and a broad low enthalpy endotherm at $173.17 \pm 0.83^\circ\text{C}$. The second broad endotherm disappeared with higher PEG ratios (data not shown). This suggests a partial to complete dissolution of NIF in PEG 1450 with increasing amount of polymer. Thus, the DSC heating process converts PM into monotectics depending on the amount of polymer present in the mixture (Friedrich et al. 2005).

The PXRD pattern of all PMs (Fig. 3a) displayed sharp crystalline peaks of NIF and PEG 1450. However, the height of NIF specific diffraction peaks were reduced and the height of PEG 1450 specific diffraction peak increased in all PMs with increase in PEG ratio. This can be attributed to the change in the fraction of NIF and PEG 1450 present in the various PMs. A statistically significant reduction in the PC of the PMs were found with an increase in the PEG 1450 fraction ($p < 0.0001$, Fig. 5, Table 1). As stated previously, PEG 1450 contains regions of low molecular

order. As higher ratios of PEG are present in the PM, the crystallinity originating from NIF is diluted and the overall PC of the PMs is decreased.

FTIR spectroscopy (Fig. 4a) was used to examine the intermolecular interactions between NIF and the polymers. As mentioned in Section 3.1, the NIF 3332 cm^{-1} , 1689 cm^{-1} , and 1679 cm^{-1} bands are sensitive to the NIF–NIF intermolecular hydrogen bonding in the NIF crystalline structure. The N–H group of NIF acts as a hydrogen bond donor (Kothari Khushboo et al. 2015) and the –OH group of PEG 1450 can participate as a hydrogen bond acceptor. All PMs showed NIF characteristic N–H (Fig. 4aI), C=O stretching vibrations (Fig. 4aII), and PEG specific –OH stretching vibrations (Fig. 4aI). This indicates that there is no interaction between NIF and PEG 1450 in their PMs. The observed PM signature peak intensities were lower than pure NIF and decreased with each increase in the PEG 1450 fraction. This decrease in intensity with increase fraction of PEG 1450 is attributed to the dilution of NIF.

A PM of NIF:PEG 1450 with HPMCAS-HF were not studied in the present study. This is because, our previous study showed that HPMCAS-HF cannot inhibit crystallization after simple physical addition (Haware et al. 2015).

3.3. Characterization of NIF and PEG 1450 SDs

A PXRD of NIF:PEG 1450 SDs are shown in Fig. 3b. As the PEG 1450 ratio increased, the characteristic NIF and PEG 1450 PXRD peaks decreased indicating a decrease in the crystallinity of both materials resulting in a lower-order SD. The PC of unexposed SDs can be arranged in the following descending order: SD NIF:PEG 1450 (1:2) > SD NIF:PEG 1450 (1:4) > SD NIF:PEG 1450 (1:10) > SD NIF:PEG 1450 (1:8) (Table 1). These differences in the crystallinity are statistically significant ($p < 0.0001$, Fig. 5).

FTIR spectroscopy (Fig. 4b) showed intermolecular hydrogen bonding between the NIF N–H group and PEG 1450 –OH group. In Fig. 4bI, the 1:8 and 1:10 NIF:PEG 1450 ratios show a significant band broadening and shift from 3332 cm^{-1} to 3412 cm^{-1} . Band broadening generally results from individual molecules hydrogen bonding to different extents. The band shift to higher wavenumbers indicates the PEG 1450:NIF hydrogen bond is weaker than the NIF:NIF intermolecular hydrogen bonds (Nie et al. 2005; Kothari K. et al. 2015). The disruption of the intermolecular NIF–NIF hydrogen bonds creates a lower-ordered NIF. This peak broadening and shift is less obvious at lower PEG 1450 ratios. Fig. 4bII further supports the observed reduction

in the order of pure crystalline NIF with the band merging of the 1679 cm^{-1} and 1689 cm^{-1} C=O group bands and a shift for the merged band to higher wave numbers (Iqbal and Chan 2015). In case of the more disordered SDs such as NIF:PEG 1450 (1:8) and NIF:PEG 1450 (1:10), the C=O specific 1679 cm^{-1} and 1689 cm^{-1} bands were merged into a single band and it was shifted to 1700 cm^{-1} (Fig. 4bII). On the other hand, the relatively higher ordered SDs like SD NIF:PEG 1450 (1:2) and SD NIF:PEG 1450 (1:4) showed two separate C=O specific bands like pure NIF. These FTIR findings corroborate the results of the PXRD studies, which shows increasing the PEG 1450 ratio produces lower-order SD matrices. Thus, hydrogen bonding is clearly involved in the amorphization process. However, the C=O specific bands were shifted to higher wavelengths, indicating weaker bonding between NIF and PEG 1450 compared to NIF:NIF bonding. Thus, it is posited that the extent of NIF:PEG 1450 interaction does not lead to complete SD amorphization.

3.4. Characterization of NIF:PEG 1450:HPMCAS-HF SDs

Fig. 4c presents the FTIR data for the NIF:PEG 1450:HPMCAS-HF SDs. Fig. 4cI shows similar band broadening and shifting of the 3332 cm^{-1} band noted for the NIF:PEG 1450 SDs (3332 cm^{-1} to 3412 cm^{-1} , Fig. 4bI). The band shift for the NIF:PEG 1450:HPMCAS-HF SDs was from 3332 cm^{-1} to 3455 cm^{-1} (Fig. 4cI). The NIF:PEG 1450:HPMCAS-HF SD hydrogen bonding band at 3455 cm^{-1} is a higher wavenumber than the NIF:PEG 1450 SD 3412 cm^{-1} band. This indicates that hydrogen bond of the HPMCAS-HF containing SD's is weaker than the NIF:PEG 1450 SDs. The observed hydrogen bonding between NIF and HPMCAS-HF is corroborated by the research of Konno and Taylor which demonstrated that NIF intercalates with HPMCAS by hydrogen bonding (Konno H. and Taylor L. S. 2008). It was also found that unlike SDs without a crystallization inhibitor, C=O group specific 1679 cm^{-1} and 1689 cm^{-1} bands were not merged into a single band (Fig. 4cII and Fig. 4cIII). Rather, these SDs exhibited a low intensity doublet bands at 1682 cm^{-1} and 1685 cm^{-1} (Fig. 4cIII). Another broad band is seen at 1700 cm^{-1} (Fig. 4cII and 4cIII). The 1700 cm^{-1} band has higher absorbance than the 1682 cm^{-1} and 1685 cm^{-1} bands. The 1702 cm^{-1} and 1682 cm^{-1} bands have been assigned previously by Konno and Taylor to non-hydrogen bonded and hydrogen bonded carbonyl groups in the felodipine, which is a structural analog of NIF (Konno and Taylor 2006). In the case of NIF, the 1700 cm^{-1} band demonstrated greater absorbance than the 1682 cm^{-1} and 1685 cm^{-1} bands. The greater absorbance of the 1700 cm^{-1} non-hydrogen bonding band relative to the 1682 cm^{-1} hydrogen bonding band strongly

suggests that hydrogen bonding between C=O group of NIF and –OH group of PEG 1450 was weakened in the presence of HPMCAS-HF. This is consistent with the observed NIF:PEG 1450:HPMCAS-HF SD 3332 cm^{-1} band shift to a higher wavenumber, indicating a weaker NIF interaction compared to NIF:PEG 1450. Interestingly, the band at 1746 cm^{-1} was found in the NIF:PEG 1450:HPMCAS-HF SDs (Fig. 4cII). This band is specific to the –COCH₃ group of HPMCAS-HF. It is conjectured that the –COCH₃ group does not undergo a significant level of hydrogen bonding with NIF in the presence of PEG 1450. Kothari et al. also observed a similar trend in NIF:PVP SDs prepared in the presence of HPMCAS (Kothari Khushboo et al. 2015). In this study, the addition of HPMCAS-HF to the dispersion tended to result in overall weaker hydrogen bonding interactions with NIF.

3.5. Preliminary physical stability studies

Statistical analysis of the solubility and PC data for the PMs, and SDs with and without HPMCAS-HF were compared by Student *t*-test and one-way ANOVA for unexposed day 0 and exposed controlled conditions after 5 days. Additionally, statistical analysis of weight loss associated with water uptake of unexposed SDs with and without HPMCAS-HF measured by TGA was performed.

The solubility comparisons of PMs and SDs are provided in Fig. 6. The one-way ANOVA indicated that the solubility of NIF in PMs, NIF:PEG 1450 SDs, and NIF:PEG 1450:HPMCAS-HF SDs were statistically different ($p<0.0001$, Fig. 6, Table 1). The Tukey's HSD post-hoc analysis showed an increase in NIF solubility with an increase in PEG 1450 fractions in the PMs ($p<0.0001$ - 0.0020). The NIF:PEG 1450 SDs demonstrated a statistically significant solubility increase compared to their PM counterparts ($p<0.0001$). This increase in solubility resulted from the amorphization of NIF to lower-order higher-energy SD matrices. Furthermore, NIF:PEG 1450:HPMCAS-HF SDs provided significantly greater NIF solubility than NIF:PEG 1450 SDs ($p<0.0001$ - 0.0403). This solubility increase can be attributed to HPMCAS-HF SDs ability to inhibit nucleation and crystallization in the dissolution media (Konno and Taylor 2006; Konno Hajime and Taylor Lynne S. 2008). The Student *t*-test demonstrated a significant decrease in the solubility of the PMs and SDs with and without HPMCAS-HF, when stored at the controlled conditions for five days ($p<0.0001$). Neither the NIF:PEG 1450 SDs nor NIF:PEG 1450:HPMCAS-HF SDs sufficiently inhibit NIF crystallization when exposed to 60% RH for 5 days. After careful review of the data, the authors do not have an explanation for the reduction in

the NIF solubility in the PMs at the controlled conditions. Although HPMCAS-HF enhanced NIF solubility to a greater extent than NIF:PEG 1450 SD alone, it did not enhance the physical stability of the SD. Therefore, the working hypothesis stating that HPMCAS-HF would provide enhanced solubility and physical stability (minimize recrystallization) compared to a NIF:PEG 1450 SD alone was rejected.

The PC of the various matrices are plotted in Fig. 5. The SDs displayed a decrease in PC compared to the PMs. The melt solvent amorphization technique was shown to be a viable process to create low-order high-energy materials. The one-way ANOVA indicated statistically significant differences in the PCs of unexposed day 0 NIF, NIF:PEG 1450, and NIF:PEG 1450:HPMCAS-HF ($p < 0.0001$, Fig. 5). Post-hoc analysis showed the PC differences between PM (1:10) and SD NIF:PEG 1450 (1:2) were statistically insignificant ($p > 0.05$). The Student *t*-test demonstrated a significant increase in the crystallinity of PM, NIF:PEG 1450 SDs, and NIF:PEG 1450:HPMCAS-HF SDs stored at the controlled storage conditions for five days ($p < 0.0001$ - 0.0089). The PC increase of the PMs after the 5 days storage period suggests that the low-order regions of PEG 1450 are crystallizing upon exposure to moisture at 60% RH. It was surprising that HPMCAS-HF did not inhibit crystallization since it has been shown to intercalate with NIF.

The percent weight loss, associated with water uptake of unexposed SDs on Day 0, at and below 100 °C, above 100 °C, and total weight loss consisting both below and above 100 °C is given in Table 2. The weight loss associated with SD 1:10 with HPMCAS-HF was obtained with two measurements and thus, it was not included in the statistical analysis. The one-way ANOVA indicated statistically significant differences in the percent weight loss of all unexposed SDs with and without HPMCAS-HF measured at and below 100 °C, above 100 °C, and total weight loss consisting both below and above 100 °C ($p < 0.0001$). The percent weight loss of SDs with and without HPMCAS-HF, having the same ratio of drug and polymer, were compared using the Tukey-Kramer HSD test. This statistical test showed significant differences measured at and below 100 °C, and above 100 °C ($p < 0.0001$ - 0.0039). Highly disordered SDs seems to sorb moisture from Day 0. The majority of weight loss associated with SDs in absence of HPMCAS-HF (between 94 to 99 % w/w of total weight loss) was observed below 100 °C. In contrast to this, higher weight loss associated with SDs in presence of HPMCAS-HF was observed above 100 °C (between 50% to 69 % w/w of total weight loss). Clearly, the water sorbed by SDs in the absence

of HPMCAS-HF seems less tightly bound than in presence of HPMCAS-HF. This can be attributed to the higher affinity of hydrophilic HPMCAS-HF towards water (Konno Hajime and Taylor Lynne S. 2008). In the absence of HPMCAS-HF, the less tightly bound water may increase the overall molecular mobility of disordered SDs. This increase in molecular mobility is thought to result in an increase in their PC (Hancock and Zografi 1997; Haware et al. 2015). However, HPMCAS-HF's ability to more tightly bind water and NIF:HPMCAS-HF bonding appears to be responsible for slowing down the crystallization of SDs. Therefore, PC of SDs containing HPMCAS-HF was significantly lower than SDs prepared without it.

4. Conclusions

The melt solvent amorphization technique using PEG 1450 and HPMCAS-HF was shown to be a viable process to create low-order high-energy NIF SDs. FTIR results showed that NIF:HPMCAS-HF intermolecular interactions were found to be weaker than NIF:PEG 1450 interactions.

The SDs of NIF with PEG 1450 prepared by the melt solvent method significantly improved NIF solubility ($p < 0.0001$) due to amorphization of NIF. This solubility was further enhanced by the addition HPMCAS-HF compared to NIF:PEG 1450 SDs ($p < 0.0001-0.0403$). A significant decrease in the solubility of the NIF:PEG 1450 SDs and NIF:PEG 1450:HPMCAS-HF SDs was found after storage at the controlled conditions for five days ($p < 0.0001$).

The prepared SDs displayed a statistically significant decrease in PC compared to their PM counterparts ($p < 0.0001$) as a result of creating lower-ordered higher-energy dispersed system matrices. The PCs of SDs with HPMCAS-HF were significantly lower than SDs not containing HPMCAS-HF. This is attributed to NIF:HPMCAS-HF bonding and the tight bonding between water and hydrophilic HPMCAS-HF which may reduce the overall molecular mobility of the disordered SDs. All SDs stored at controlled conditions for five days exhibited a significant increase in PC ($p < 0.0001-0.0089$).

The results of the present study revealed that although HPMCAS-HF improves the solubility of NIF, it does not provide crystal growth inhibition of NIF:PEG 1450:HPMCAS-HF SDs.

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Figure 1 Structure of nifedipine

Figure 2: Open pan differential scanning calorimetry of NIF, PEG 1450, HPMCAS-HF, and physical mixture (PM) of NIF:PEG (1:2). **[b]** Thermogravimetric analysis of NIF, PEG 1450, and HPMCAS-HF.

Figure 3. Powder x-ray diffraction pattern of **[a]** NIF, PEG 1450, and their PM, **[b]** NIF:PEG 1450 solid dispersions (SD), and **[c]** NIF:PEG 1450:HPMCAS-HF SDs.

Figure 4. Fourier transform infrared spectra of **[a]** NIF, PEG 1450, and their PM, **[b]** NIF:PEG 1450 (1:2, 1:4, 1:8, and 1:10) SD **[c]** NIF:PEG 1450 (1:2, 1:4, 1:8, and 1:10: plus HPMCAS-HF) SD . (I) 3332 cm^{-1} spectra; (II) 1689 cm^{-1} and 1679 cm^{-1} spectra; (III) 1701 cm^{-1} and 1682 cm^{-1} spectra.

Figure 5. Percent crystallinity comparison of NIF, PM of NIF and PEG 1450, SD of NIF and PEG 1450 with and without HPMCAS-HF in different ratios exposed at different time intervals. [n=3; Each error bar is constructed using a 95% confidence interval of the mean.]

Figure 6. Solubility comparison of PM of NIF and PEG 1450, SD of NIF and PEG 1450 with and without HPMCAS-HF in different ratios exposed at different time intervals. [n=3; Each error bar is constructed using a 95% confidence interval of the mean.]

Table 1 NIF solubility ($\mu\text{g/mL}$) and percent crystallinity (%) in PM and SD

Table 2 Percent weight loss associated water content of solid dispersions measured by thermogravimetric analysis at Day 0

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Table 1 NIF solubility ($\mu\text{g/mL}$) and percent crystallinity (%) in PM and SD

Components/Formulations	NIF solubility ($\mu\text{g/mL}$) ^a		Percent crystallinity (%)	
	0 day	5 days (25 °C /60% RH)	0 day	5 days (25 °C /60% RH)
NIF	5.52 $\pm$ 0.02	2.22 $\pm$ 0.05	98.28 $\pm$ 0.28	99.91 $\pm$ 0.06
PM NIF:PEG (1:2)	5.00 $\pm$ 0.00	0.97 $\pm$ 0.00	83.66 $\pm$ 1.41	87.74 $\pm$ 0.45
PM NIF:PEG (1:4)	5.35 $\pm$ 0.01	1.48 $\pm$ 0.01	81.09 $\pm$ 0.61	84.15 $\pm$ 0.12
PM NIF:PEG (1:8)	5.51 $\pm$ 0.00	2.00 $\pm$ 0.02	77.01 $\pm$ 0.62	81.52 $\pm$ 0.91
PM NIF:PEG (1:10)	6.73 $\pm$ 0.03	2.71 $\pm$ 0.02	72.84 $\pm$ 0.25	79.72 $\pm$ 0.08
SD NIF:PEG (1:2)	7.97 $\pm$ 0.13	4.93 $\pm$ 0.03	72.91 $\pm$ 0.12	77.89 $\pm$ 0.04
SD NIF:PEG (1:4)	9.16 $\pm$ 0.01	4.10 $\pm$ 0.00	58.36 $\pm$ 0.36	60.58 $\pm$ 0.21
SD NIF:PEG (1:8)	13.31 $\pm$ 0.01	5.02 $\pm$ 0.01	26.50 $\pm$ 0.20	40.76 $\pm$ 0.58
SD NIF:PEG (1:10)	12.75 $\pm$ 0.03	5.08 $\pm$ 0.03	28.28 $\pm$ 0.27	37.94 $\pm$ 0.09
SD NIF:PEG (1:2) + HPMCAS-HF	8.09 $\pm$ 0.00	5.34 $\pm$ 0.02	30.87 $\pm$ 0.19	44.32 $\pm$ 1.46
SD NIF:PEG (1:4) + HPMCAS-HF	10.10 $\pm$ 0.01	5.86 $\pm$ 0.01	26.70 $\pm$ 0.22	39.74 $\pm$ 0.15
SD NIF:PEG (1:8) + HPMCAS-HF	14.59 $\pm$ 0.01	6.08 $\pm$ 0.02	23.16 $\pm$ 0.24	36.65 $\pm$ 0.07
SD NIF:PEG (1:10) + HPMCAS-HF	22.02 $\pm$ 0.02	7.24 $\pm$ 0.04	15.37 $\pm$ 0.26	23.80 $\pm$ 0.18

^amean $\pm$ standard deviation; $n=3$.**Table 2:** Percent weight loss associated water content of solid dispersions measured by thermogravimetric analysis at Day 0

Sample name	First Weight Loss <100 °C (%)	Second Weight Loss >110 °C (%)	Total Weight Loss (%)
SD NIF:PEG (1:2)	10.154 (0.735)	0.573 (0.717)	10.727 (1.251)
SD NIF:PEG (1:4)	10.178 (1.509)	0.165 (0.083)	10.344 (1.493)
SD NIF:PEG (1:8)	17.664 (2.507)	0.215 (0.112)	17.879 (2.546)
SD NIF:PEG (1:10)	13.151 (3.063)	0.111 (0.044)	13.262 (3.019)
SD NIF:PEG (1:2)+HPMCAS-HF	2.975 (0.558)	3.063 (0.639)	6.038 (0.693)
SD NIF:PEG (1:4)+HPMCAS-HF	3.091 (0.567)	8.672 (2.223)	11.763 (2.320)
SD NIF:PEG (1:8)+HPMCAS-HF	5.400 (3.011)	10.727 (4.305)	16.127 (7.219)
SD NIF:PEG (1:10)+HPMCAS-HF	5.145* (0.179)	11.970* (0.721)	17.115* (0.542)

[$n=3$; Values in parenthesis indicates standard deviation; * indicated average of two measurements]