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RESEARCH PAPER

Effect of Water-Soluble Carriers on Dissolution Characteristics of Nifedipine Solid Dispersions

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ABSTRACT

Solid dispersions of nifedipine (NP) with polyethylene glycols (PEG4000 and PEG6000), hydroxypropyl-β-cyclodextrin (HPβCD), and poloxamer 407 (PXM 407) in four mixing ratios were prepared by melting, solvent, and kneading methods in order to improve the dissolution of NP. The enhancement of the dissolution rate and the time for 80% NP dissolution $T_{80\%}$ *depended on the mixing ratio and the preparation method. The highest dissolution rate and the* $T_{80\%}$ *as short as 15 min were obtained from PXM 407 solid dispersion prepared by the melting method at the mixing ratio of 1:10. The X-ray diffraction (XRD) patterns of solid dispersions at higher proportions of carriers demonstrated consistent with the results from differential scanning calorimetric (DSC) thermograms that NP existed in the amorphous state. The wettability and solubility were markedly improved in the PXM 407 system. The presence of intermolecular hydrogen bonding between NP and PEGs and between HPβCD and PXM 407 was shown by infrared (IR) spectroscopy.*
Key Words: *Amorphous; Dissolution; Nifedipine; Poloxamer; Solid dispersion.*

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INTRODUCTION

Nifedipine (NP), a calcium channel blocker, is useful in the treatment of cardiovascular disorders, including hypertension and angina pectoris (1). Since NP is practically water insoluble, its bioavailability is low when administered orally as the crystalline form (2). The possibility of improving the solubility and dissolution rate by the transformation to the amorphous state seems to be attractive. Solid dispersions of NP by some water-soluble carriers were found to enhance drug dissolution (3–5) and consequently bioavailability (6,7).

Polyethylene glycols (PEGs), one of the predominant polymers, were extensively used in the solid dispersions. NP-PEG6000 solid dispersions prepared by the melting method resulted in a greater increase of dissolution than PEG4000 solid dispersions (4,8). 2-Hydroxypropyl-β-cyclodextrin (HPβCD), a cyclic oligosaccharide composed of seven glucose units, has been widely applied to enhance solubility, dissolution, and stability of various drugs via complexation (8–15). Recently, poloxamers (PXMs), a group of nonionic surfactants, have been drawn for solid dispersion application. Dissolution improvement of slightly soluble drugs (e.g., digitoxin and digoxin) was reported (16).

It was interesting to study the enhancing effect of a widely used block copolymer surfactant, poloxamer 407, on the dissolution characteristics of NP compared with well-known solid dispersing carriers, PEGs (PEG4000 and PEG6000) and HPβCD. The effects of preparation methods and drug-to-carrier mixing ratios were investigated. Moreover, mechanisms of fast release of NP solid dispersions were characterized by studies of solubility, wettability, powder X-ray diffraction (XRD) analysis, differential scanning calorimetry (DSC), infrared (IR) spectroscopy, and scanning electron microscopy (SEM).

EXPERIMENTAL

Materials

Nifedipine was kindly donated by Moehs, S. A., Barcelona, Spain. PEGs (Lutrol E4000 and Lutrol E6000) and Poloxamer 407 (Lutrol F127) were gifts from BASF (Thai), Limited. 2-Hydroxypropyl-β-cyclodextrin was purchased from Fluka Chemie AG, Buehs, Switzerland. All other chemicals were analytical reagent grade. All experiments were carried out under subdued light and low-pressure sodium lamp radiation to prevent photodegradation of NP (17,18).

Methods

Preparation of Solid Dispersion Systems

The physical mixtures were prepared by mixing NP and the carriers continuously for 5 min at drug:carrier ratios of 1:1, 1:3, 1:5, and 1:10 using a glass mortar and pestle.

Melting Method

The physical mixtures were heated at 70°C–80°C until completely melted. The molten mixture was then cooled rapidly in an ice bath and solidified.

Solvent Method

Nifedipine was first dissolved in a small volume of acetone and then thoroughly mixed with 100 ml of ethanolic solution of carriers in a round-bottom flask. The solvent was evaporated under reduced pressure at 40°C (rotary evaporator RE120, Büchi, Flawil, Switzerland).

Kneading Method

The physical mixtures were incorporated with appropriate amounts of deionized water (0.1 times of total weight for PEGs and PXM 407 and 0.4 times for HPβCD) in a mortar and pestle and kneaded for 30 min. The kneaded masses were sieved through 30 mesh and dried at 45°C for 1 day.

All samples, after pulverization and sieving through 60 mesh, were protected from light and kept in a vacuum desiccator through the experimental period. Triplicate assays were carried out for drug content by the spectrophotometric method (Jasco UV/Vis spectrophotometer, model 7800) at 238 nm and 280 nm (19).

Solubility

Excess amounts of NP were added to 5 ml distilled water containing various concentrations of carriers (20). After vertical rotation for 24 hr at 30°C, samples were withdrawn, filtered through an 0.8-μm membrane filter, diluted with methanol, and analyzed by the spectrophotometric method (19).

Dissolution

Dissolution tests according to USP23 using apparatus 2 were carried out at 37°C and at a rotary speed of 150

rpm. Samples equivalent to 10 mg NP were placed in 900 ml simulated gastric fluid without pepsin (pH 1.2). At specified times, 5-ml samples were withdrawn, filtered through an 0.8-μm membrane filter, and assayed by the spectrophotometric method. Fresh medium was added to maintain a constant volume after each sampling. Triplicate runs were carried out. Dissolution rate constants at the initial 30 min and the time for 80% NP dissolution $T_{80\%}$ were determined.

Wettability

Sample powders (200 mg) were compressed into a pellet by a hydraulic press at 400 psi for 1 min. Water (20 μl) was dropped from a microsyringe on the pellet surface. After 2 s, the drop was photographed; the contact angle could be measured directly from the photograph (21). Triplicate studies were carried out.

Powder X-Ray Diffraction

The powder XRD patterns were investigated on a Rigaku Denki diffractometer (MiniFlex 2027, Tokyo, Japan) with copper target and nickel filter at 30 kV, 5 mA current, 4°/min scanning speed, and 5°–40° (2θ) range.

Differential Scanning Calorimetry

The DSC thermograms were investigated on a Du Pont differential scanning calorimeter (model TA9900, New Castle, USA) using 2–3 mg samples in a closed aluminum pan at a scanning speed of 5°C/min in the temperature range 35°C–250°C under a nitrogen gas flow of 60 ml/min.

Infrared Spectrophotometry

Infrared spectra were investigated on a Perkin-Elmer Fourier transform infrared (FTIR) spectrophotometer (Spectrum 2000, CT, USA) by the KBr disk method from 4000 to 400 cm^{-1}.

Scanning Electron Microscopy

SEM was performed using a JSM-6400 (Jeol, Japan) by coating the samples with gold using ion sputtering.

RESULTS AND DISCUSSION

Dissolution Enhancement of Nifedipine

Figure 1 illustrates the dissolution patterns of NP from various solid dispersion systems, including the dissolution pattern from NP crystals. As the 1:10 (NP:carrier) mixing ratio showed the most significant effects on dissolution improvement, the profiles of the 1:10 ratio with different preparation methods are illustrated. Since the PEG4000 and PEG6000 systems showed similar patterns of NP dissolution, only the patterns from PEG6000 systems were depicted.

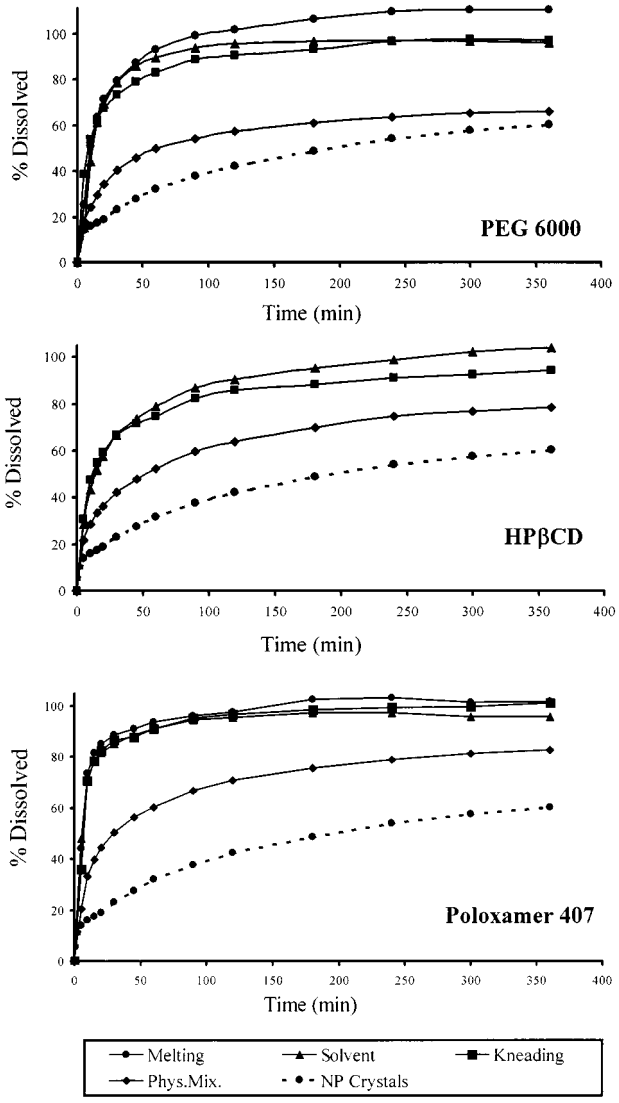


Figure 1. Dissolution of nifedipine from solid dispersions with PEG6000, hydroxypropyl-β-cyclodextrin (HPβCD), and poloxamer 407 prepared by different methods at a 1:10 ratio at 37°C.

Physical mixtures had slightly improved dissolution patterns compared with those for the NP crystals. The solid dispersions, however, showed marked improvement

in NP dissolution; even the melting solid dispersion was not able to prepare for the HPβCD system. As the PXM 407 system showed the fastest and most complete dissolution pattern, the effects of the drug mixing ratio on the pattern are illustrated in Fig. 2 using PXM 407 solid dispersion prepared by the solvent method. As the carrier contents increased, the dissolution improvement was clear. At the lower mixing ratios of 1:1 and 1:3, the NP dissolution was less improved than at the higher ratios of 1:5 and 1:10. In PEGs and HPβCD systems, the 1:10 mixing ratio also showed the highest dissolution profile. Save and Venkitachalam (4) reported the highest improvement of NP at a 1:10 ratio of NP:PEGs, and that NP existed in an amorphous state from the XRD pattern. When the proportion of PEGs increased, the dissolution was suppressed, probably due to the increase of viscosity in the diffusion layer.

The dissolution rate constants for the initial 30 min were determined by plotting the logarithm of the percentage undissolved versus time. Good linear relationships were obtained, indicating a first-order dissolution process. The effects of the preparation methods and the mixing ratios on dissolution rate constants and the time for 80% drug dissolution ($T_{80\%}$) for all systems are compared in Fig. 3. In all carriers, solid dispersions had greater dissolution rates than their corresponding physical mixtures and NP crystals, for which the dissolution rate constant was 0.0287 min^{-1}. The dissolution rates of NP from solid dispersions depended on the mixing proportion and on the preparation method.

To clarify the differences in dissolution rates, two-way analysis of variance (ANOVA) was performed for all solid dispersion systems. For the PEG4000 system, the melting, solvent, and kneading methods had equivalent effects and were similarly superior to the physical mixture ($p < .05$). The 1:10 mixing ratio of the melting and solvent methods showed the fastest rate, 4.3-fold and 4.1-fold of that of intact NP crystals, respectively ($p < .05$). For the PEG6000 system, the melting and solvent methods gave higher rates than the kneading method and the physical mixture ($p < .05$). The 1:10 mixing ratio of the PEG6000 system prepared by the melting and solvent methods significantly yielded the fastest rate, 4.4-fold and 4.5-fold that of NP crystals, respectively ($p < .05$). It was shown that NP-PEG6000 solid dispersions resulted in greater enhancement of dissolution than PEG4000 solid dispersions. Higher molecular weight PEG was more viscous to the system and thereby presumably reduced drug crystallization (21). These results showed higher dissolution improvement than those reported by Law et al. (6), for which the 2.6-fold increase of NP initial dissolution rate was obtained from NP solid dispersion with combined PEG and phosphatidylcholine. For the HPβCD system, the kneading method gave the fastest rate ($p < .05$). The 1:10 mixing ratio showed a significantly high rate, with a 3.8-fold increase compared to NP crystals ($p < .05$). Recently, HPβCD was reported to give a higher relative dissolution potency than β-cyclodextrin. β-Cyclodextrin derivatives have high affinity to the hydrophobic drug and can interact strongly due to their amphiphilic nature (22). For the PXM 407 system, the most remarkable dissolution improvement for NP was observed. The melting method was significantly superior to the others ($p < .05$). The 1:10 mixing ratio of the melted sample gave the fastest rate, as high as 5.9-fold of the NP crystals. Mura et al. (23) reported the beneficial effects of the incorporation of surfactants (sodium dodecyl sulfate and Tween 80) into naproxen-PEG solid dispersions. The best performance given by the surfactants has been attributed to several factors, such as high hydrophilicity, good solubilizing power, and facile interaction with drug molecules.

Since the USP23 states, in the monograph of nifedipine soft capsules containing NP in solution form, that not less than 80% NP should be dissolved in 20 min, the time for 80% dissolution $T_{80\%}$ was examined. It was interesting that only PXM 407 was in accordance with the compendial requirement. The solid dispersions of PXM 407 prepared by the melting method in the 1:3, 1:5, and 1:10 mixing ratios exhibited a $T_{80\%}$ of 15 min. The relative dissolution potency of the investigated carriers might be in the order PXM 407 > PEG6000 > HPβCD > PEG4000.

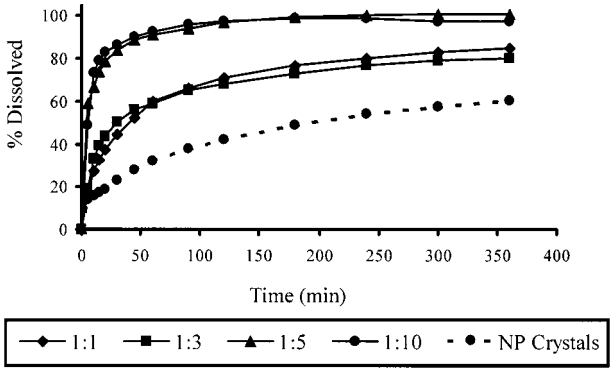


Figure 2. Effect of drug:carrier mixing ratio on nifedipine dissolution from the solid dispersion with poloxamer 407 prepared by the solvent method at 37°C.

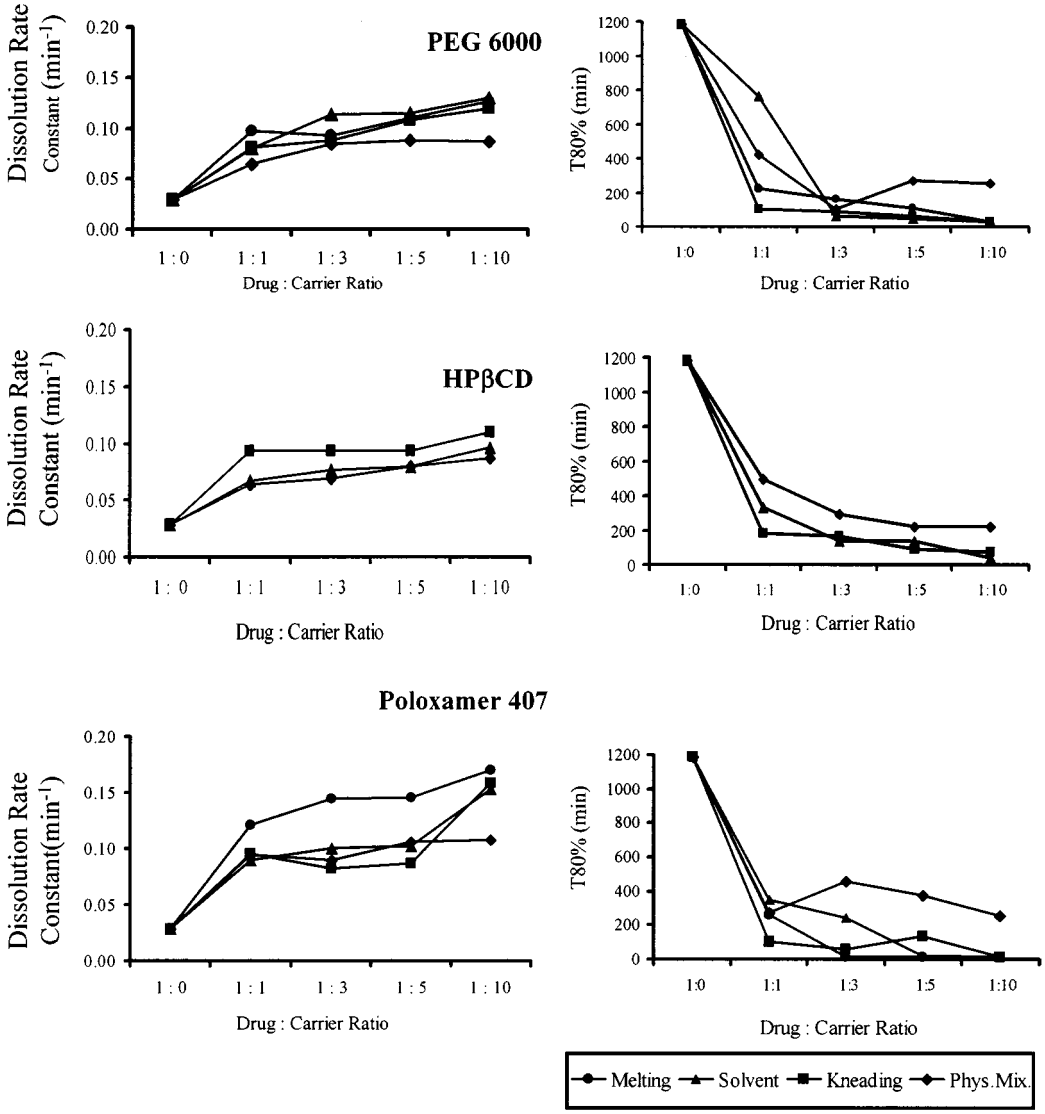


Figure 3. Effect of preparation methods and mixing ratios on nifedipine dissolution rate constant and $T_{80\%}$ from solid dispersions with PEG6000, hydroxypropyl-β-cyclodextrin (HPβCD), and poloxamer 407.

Solubility

The solubility of NP in distilled water at 30°C was observed as 8.0 μg/ml. It was shown that PEG4000, PEG6000, and HPβCD had nearly the same extent of solubilizing effects (Fig. 4). This solubilization was obtained from PXM 407. There was a minimum concentration of PXM407 to exhibit the solubility enhancement at approximately 0.8%. This might attributed to the surface active property, thus demonstrating the critical micelle concentration. At a concentration of 4% PXM 407, the solubility was increased by 27-fold of that in distilled water and 15-fold of that in the presence of other carriers. As PXM 407 is a polyoxyethylene-polypropylene block copolymer nonionic surfactant with an HLB (hydrophilic-lipophilic balance) value of 18–23, and is used as a potential solubilizer for certain active substances and essential oils in pharmaceutical preparations (24), some molecular interaction between PXM 407 and NP should occur. Shin and Cho (25) reported an increased aqueous

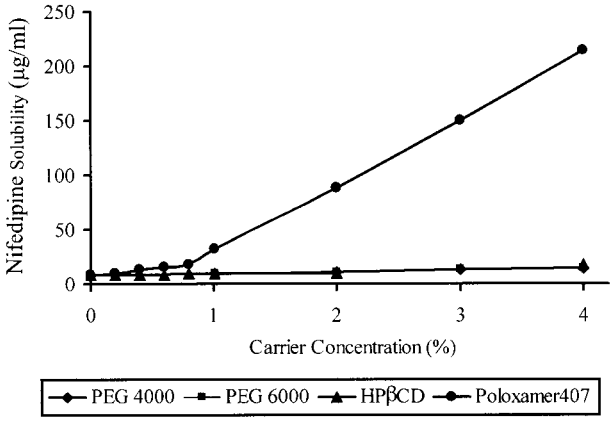


Figure 4. Effect of carrier concentration on the solubility of nifedipine at 30°C.

solubility of piroxicam by about 11-fold at a concentration of 22.5% by weight of PXM 407. From their study, the IR spectroscopic analysis showed an association between functional groups of piroxicam and PXM.

Wettability

Nifedipine is hydrophobic with a contact angle of 85°. As shown in Fig. 5, the contact angles in the solid dispersions were smaller than that of NP. The preparation methods and mixing ratios seemed to have a slight effect on the wettability. It was found that the PEG4000 system exhibited the highest wettability, whereas PXM 407 showed the lowest. Consequently, it might be said that enhanced dissolution of NP from the solid dispersions might be due partly to the increase in drug wettability.

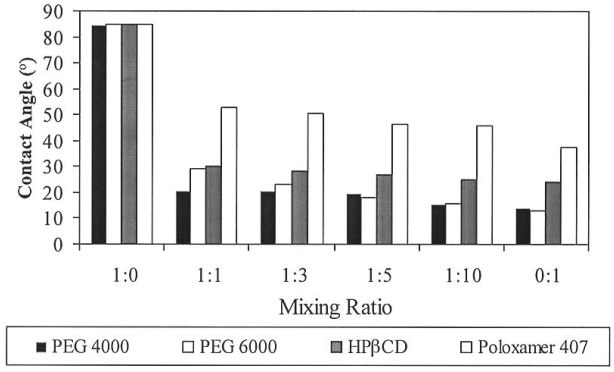


Figure 5. Contact angle of nifedipine solid dispersions with PEG4000, PEG6000, hydroxypropyl-β-cyclodextrin (HPβCD), and poloxamer 407 prepared by the solvent method.

Powder X-ray Diffraction

The XRD patterns of NP PEGs, HPβCD, and PXM 407 the physical mixtures and the solid dispersions are illustrated in Fig. 6. Nifedipine was a highly crystalline powder with characteristic diffraction peaks at 2θ of 8.0°, 11.9°, 16.2°, 19.5°, and 24.0°. Due to the similar patterns of XRD for PEG4000 and PEG6000, only PEG4000 systems were demonstrated. The XRD patterns of PEG4000 showed two characteristic peaks of high intensity, at 19.5° and 23.5°. The PEG polymers are semicrystalline, containing both ordered and amorphous components (26). Poloxamer 407 had an XRD pattern with two diffraction peaks, at 19.3° and 23.4°, while HPβCD showed a halo pattern, indicating an amorphous form.

In the PEG systems, the physical mixtures possessed the diffraction peaks of both PEGs and NP crystals, indicating that NP was in the crystalline state. The XRD patterns of NP-PEG solid dispersions prepared by the melting method showed the absence of peaks corresponding to NP crystals at the 1:10 mixing ratio. This indicated that NP was converted to an amorphous form. On the other hand, the solid dispersions prepared by the solvent and kneading methods showed weak NP diffraction peaks. These data indicated that a small portion of NP might crystallize during the processing and existed in the microcrystalline form (4). The enhancement of dissolution from the solid dispersions may be attributed partly to the transformation of the NP crystalline state to the high-energy, unstable state in the crystalline PEGs (27).

In contrast to the PEG systems, the diffraction peaks of NP crystals disappeared in the coevaporates of NP-HPβCD with a higher mixing ratio than 1:3, indicating that NP was converted to an amorphous state or included state. However, the kneading sample and the physical mixture at 1:10 ratio still showed diffraction peaks corresponding to NP crystals. Similar results with PEG systems were observed in the PXM 407 system. The melt of 1:10 mixing ratio showed the absence of diffraction peaks of NP crystals, and the much decreased crystallinity of NP was obtained in the PXM 407 solid dispersions prepared by the solvent and kneading methods.

Differential Scanning Calorimetry

The DSC thermograms of NP, PEGs, the solid dispersions, and the physical mixtures are shown in Fig. 7. The NP crystals gave the melting endotherm at 174.8°C. All PEG4000 and PEG6000 solid dispersions and the physical mixtures exhibited the sharp endothermic peaks due

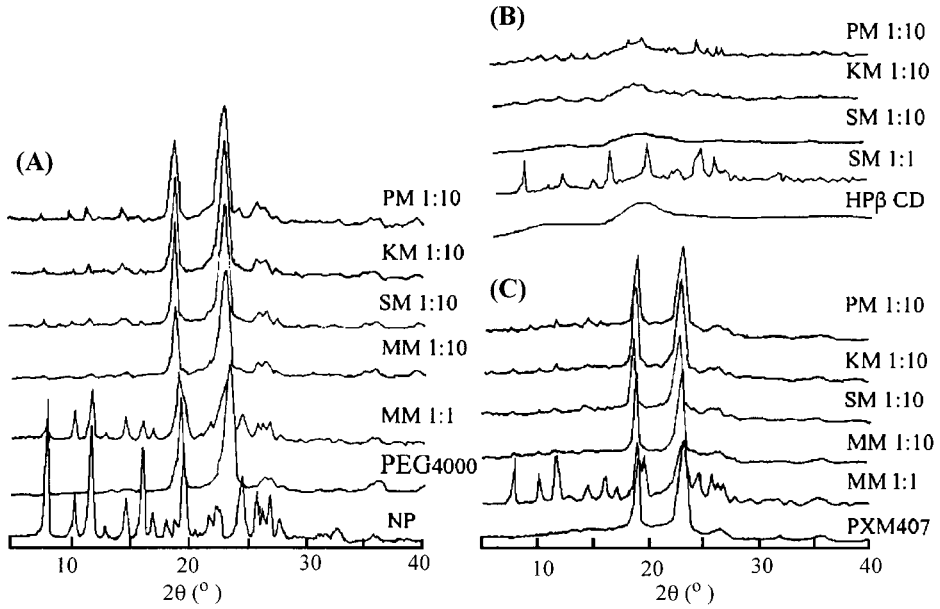


Figure 6. X-ray diffraction patterns of nifedipine, PEG4000, hydroxypropyl-β-cyclodextrin (HPβCD), and poloxamer 407 solid dispersions prepared by the melting method (MM), solvent method (SM), kneading method (KM), and physical mixtures (PM): (A) PEG4000; (B) hydroxypropyl-β-cyclodextrin; (C) poloxamer 407.

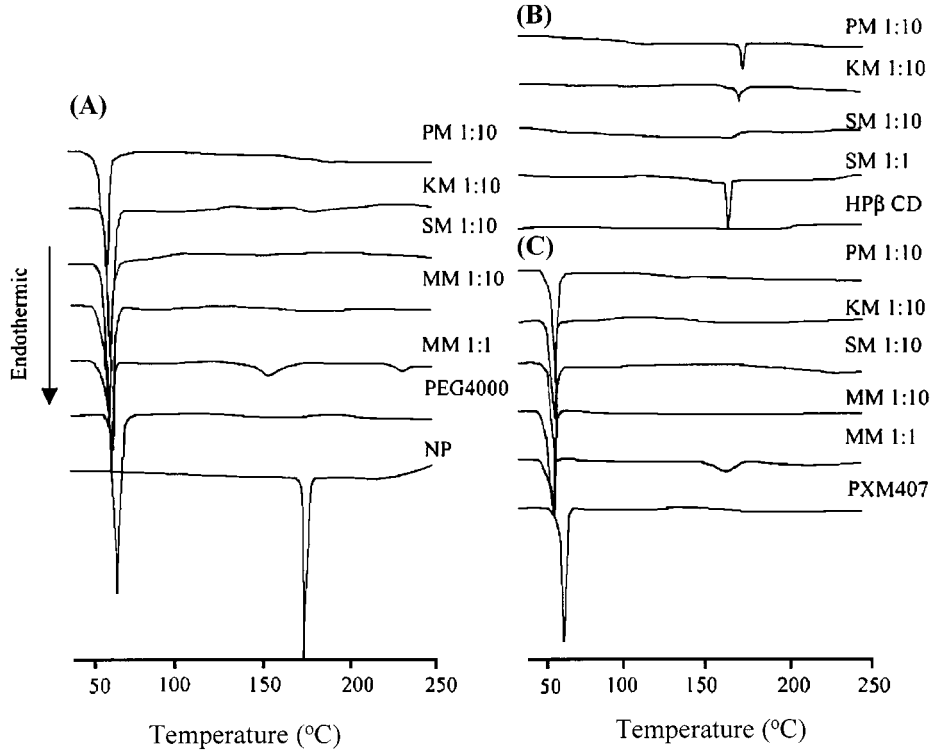


Figure 7. Differential scanning calorimetric curves of nifedipine, PEG4000, hydroxypropyl-β-cyclodextrin, and poloxamer 407 solid dispersions prepared by the melting method (MM), solvent method (SM), kneading method (KM), and physical mixtures (PM): (A) PEG4000; (B) hydroxypropyl-β-cyclodextrin; (C) poloxamer 407.

to the fusion of PEG4000 and PEG6000 at around 57°C–62°C. This revealed the existence of PEGs in the crystalline state that was consistent with the appearance of the diffraction peaks in the corresponding XRD patterns. The melting of NP was observed in the physical mixtures and in the solid dispersions of lower mixing ratios as broad endotherms at a temperature range lower than the melting point of NP crystals. The disappearance of NP melting endotherms was observed in all NP-PEG solid dispersions of the 1:10 ratio. These results might suggest that the enhancement of NP dissolution was attributed to the conversion of NP to an amorphous state in crystalline PEGs.

The absence of NP melting peak was observed in the thermogram of HPβCD solid dispersion prepared by the solvent method at the 1:10 mixing ratio. This result was consistent with the XRD studies that NP existed in HPβCD coevaporates in an amorphous form. However, the melting endotherms of NP were observed in the solid dispersions prepared by the kneading method of all mixing ratios and physical mixtures. For the PXM 407 system, results similar to those with the PEG systems were obtained. The melting peak of NP was not observed from the thermograms of the solid dispersions prepared from all methods at the 1:10 mixing ratio, including the corresponding physical mixture.

Infrared Spectroscopy

The IR spectra of NP, carriers, the solid dispersions, and the physical mixtures are illustrated in Fig. 8. The absorption band of N–H stretching vibration of NP at 3331 cm^{-1}, C–H aromatic vibration at 3102 cm^{-1} and C–H aliphatic stretching at 2954 cm^{-1} were observed. The major peaks of C═O stretching were at 1689 and 1680 cm^{-1} and C–O ester stretching at 1228 and 1122 cm^{-1}. The sharp peak of NO_2 stretching was observed at 1530 cm^{-1}.

Due to the similarity of the molecular structure, PEG4000 and PEG6000 showed similar absorption spectra, in which a characteristic broad peak of O–H stretching vibration from 3300 to 3600 cm^{-1}, C–H stretching of OC_2H_5 groups from 2800 to 2900 cm^{-1} and C–O stretching from 1000 to 1200 cm^{-1} were observed. The solid dispersions of both PEGs, especially at the lower proportions of PEG, showed IR spectra similar to those of their corresponding physical mixtures. They showed the superimposed spectra of NP crystals and PEGs. At the higher proportions of PEG, the absorption intensities of some NP bands were reduced markedly. The N–H stretching band of NP at 3331 cm^{-1} disappeared in the spectra of the melt with PEGs at the 1:10 mixing ratio, and the broad O–H stretching band of PEGs slightly

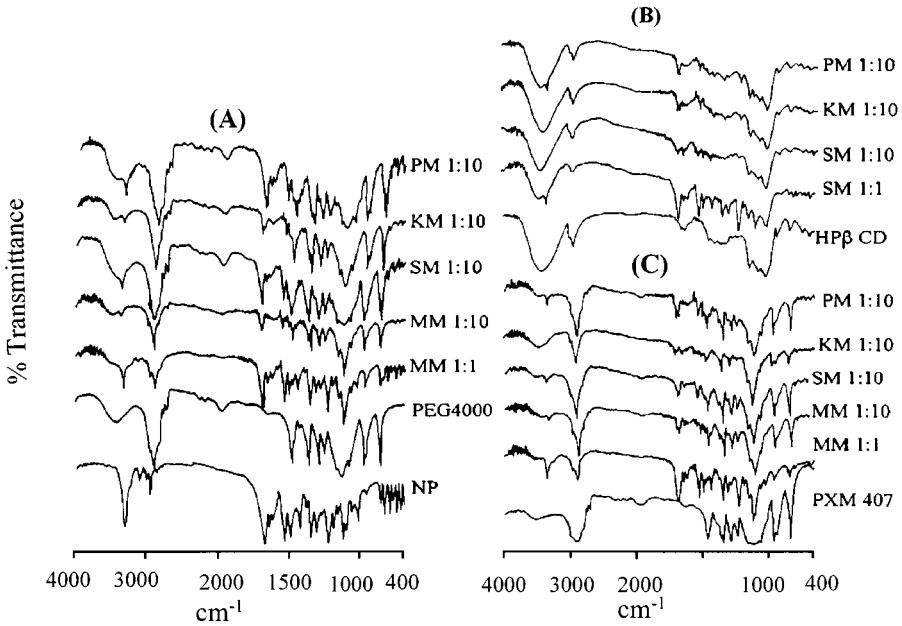


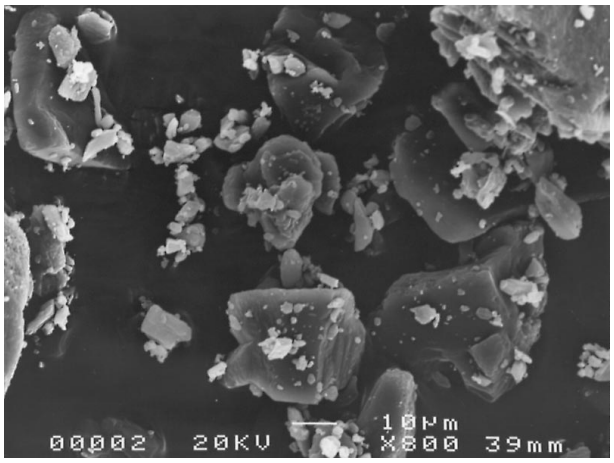
Figure 8. Infrared spectra of nifedipine, PEG4000, hydroxypropyl-β-cyclodextrin (HPβCD), and poloxamer 407 solid dispersions prepared by the melting method (MM), solvent method (SM), kneading method (KM), and physical mixtures (PM): (A) PEG4000; (B) hydroxypropyl-β-cyclodextrin; (C) poloxamer 407.

shifted to the lower frequency. It might be speculated that the intermolecular hydrogen bonding between NP and PEG molecules existed (28). All observations from the PEG systems were also obtained from PXM 407; this might be due to the similarity of the groups of polymers (24,26).

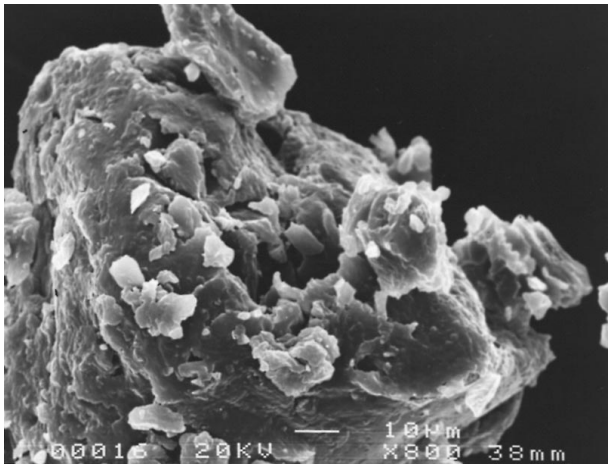
HPβCD showed the very intense O–H stretching band at 3000–3600 cm^{-1}. The C–H stretching was at 2930 cm^{-1}, and the C–O stretching of primary and secondary O–H groups was observed at 1033 and 1156 cm^{-1}, respectively. Similar to the PEGs and PXM 407 systems, the solid dispersions from the solvent method at the 1:10 ratio showed the absence of the N–H stretching band at 3331 cm^{-1}, suggesting the intermolecular hydrogen bonding between the drug and the carrier.

Scanning Electron Microscopy

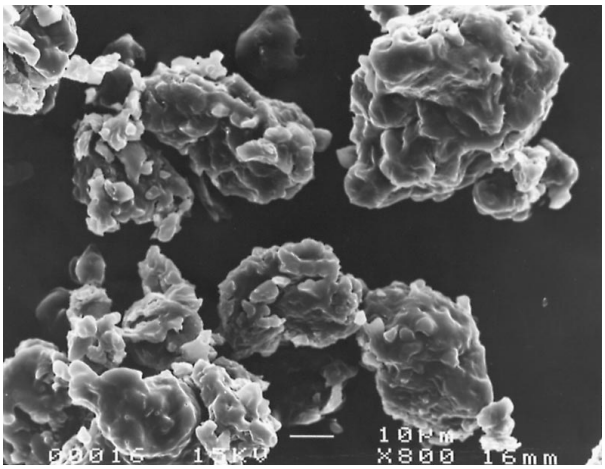
Since PXM 407 exhibited the most remarkable enhancing effect on NP dissolution, some photomicrographs of the polymer are shown in Fig. 9. Nifedipine crystals exhibited a smooth surface and were relatively



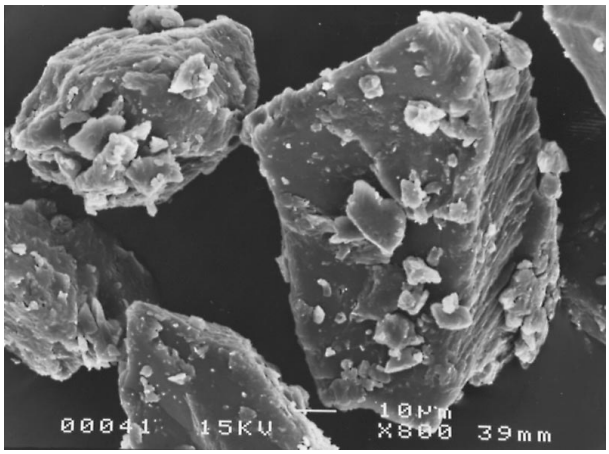
NP Crystals



PXM 407



NP-PXM 407 Melt, 1:10 Ratio



NP-PXM 407 Physical Mixture, 1:10 Ratio

Scale |—| 20 µm

Figure 9. Scanning electron micrographic images of nifedipine:poloxamer 407; solid dispersion prepared by melting method and physical mixture at the 1:10 ratio (×800).

smaller than those of PXM 407 particles. Nifedipine particles could be adsorbed physically and dispersed on the carrier particle surfaces in the physical mixtures. As the photomicrograph of the melt showed the homogeneity, NP molecules should be dispersed uniformly in the carrier matrices. The solid dispersion technique reduced drug aggregates and agglomerates and had an advantage over traditional physical size reduction (27).

CONCLUSIONS

Solid dispersions of NP in PEGs, HPβCD, and PXM 407 improved the dissolution rate of nifedipine. The relative dissolution potency of the carriers might be ranked as PXM 407 > PEG6000 > HPβCD > PEG4000. Effects of the preparation methods and the mixing ratios on the dissolution were clearly observed. The physicochemical characterization by XRD and DSC studies revealed that the enhancing effect of solid dispersions on the dissolution was mainly attributed to the transformation of NP into the amorphous state. Improvement of wettability and increased solubility also contributed to the results. In addition, the IR spectra indicated the possible intermolecular hydrogen bonding between the drug and the carriers.

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