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RESEARCH PAPER

Enhanced Solubility Through Particle Size Control, Modification of Crystal Behavior, and Crystalline Form Changes in Solid Dispersion of Nifedipine

Ju young Jung, Kwang Il Shin, Minseon Lee, Myeongkwan Song, and Soonjo Kwon

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Abstract The purpose of this study was to investigate the selectivity of polymers and the suitability of spray drying to enhance nifedipine solubility. Nifedipine alone or in combination with polymers was dissolved in a mixed solvent of methylene chloride and ethanol. The hydrophilic polymers used were PVP K-30, HPMC, HPMCP, Eudragit, and HPMCAS. Each solid dispersion was prepared using a laboratory spray dryer. The spray-dried solid dispersants were characterized by SEM, DSC, and XRPD analysis, and dissolution tests compared the dissolution rates of nifedipine solid dispersants and nifedipine. The results showed that all spray-dried solid dispersions were in an amorphous form. Dissolution tests were performed at pH 1.2 (artificial gastric juice) and pH 6.8 (artificial intestinal juice) to evaluate solid dispersion solubility. The solid dispersion containing HPMC showed a notably enhanced dissolution rate under both pH conditions. Interestingly, HPMCP and HPMCAS showed almost no enhancement of dissolution behavior at pH 1.2, but a significant increase (10 times or higher) over that of the pure polymer at pH 6.8. Solubility enhancement of poorly soluble drugs differs markedly among the polymers used for spray drying. From the results, HPMCP and HPMCAS are suitable as carriers for drugs with poor solubility that require acid resistance.

Ju young Jung, Kwang Il Shin
Green Materials Division, Lotte Fine Chemical, Incheon 21700, Korea

Ju young Jung, Minseon Lee, Myeongkwan Song, Soonjo Kwon*
Department of Biological Engineering, Inha University, Incheon 22212, Korea
Tel: +82-32-860-9176; Fax: +82-32-872-4046
E-mail: soonjo.kwon@inha.ac.kr

Ju young Jung, Minseon Lee, Myeongkwan Song, Soonjo Kwon
Department of Biological Sciences and Bioengineering, Inha University, Incheon 22212, Korea

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1. Introduction

Poorly soluble drugs have a very low solubility in water, resulting in problems associated with insufficient bioavailability or absorption of the drug. Methods for improving the solubility of drugs, such as controlling the particle size of poorly soluble drugs, modifying crystal behavior, and changing the crystal form, have been used to overcome such problems [1]. Among these methods, enhancement of drug solubility by using a solid dispersion is the most commonly used drug solubilization method [2].

Spray drying is an important process used in the pharmaceutical industry to improve a wide range of drug formulation and drug delivery problems. In general, it can be used for dry powder production in liquid form, microencapsulation, the development of microspheres or microcapsules, and improving storage stability by using it as a preservation method for solutions, suspensions, and emulsions, which may be the initial aqueous formulation. A solid dispersion is a uniform dispersion of a poorly soluble drug in a molecular-sized polymer carrier [3]. To prepare an effective solid dispersion, the type and molecular weight of the polymer, the crystallinity and solubility of the drug, and the drug's recrystallization properties should be considered; moreover, process parameters related to the porosity and hygroscopicity of the solid dispersion particles should be appropriately adjusted [4,5].

Nifedipine, the drug investigated in this study, is an antihypertensive agent and a calcium antagonist that selectively blocks only calcium ion inflow through cells of the

myocardium and vascular fascia [6]. However, nifedipine is a poorly soluble drug and, in addition to the disadvantage of having very low solubility in water, is light sensitive. To enhance the low solubility, solid dispersions were prepared using various polymers in this study. Solid dispersions can comprise a poorly soluble drug bound to a polymer, with the subsequent drug-release properties of the dispersion determined by the properties of the polymer used. Generally, the polymers used are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polymethacrylate, hypromellose (HPMC), or cellulose derivatives such as ethylcellulose (EC) and hydroxypropyl cellulose (HPC), or starch derivatives such as cyclodextrin [4,6-10]. The role of the polymer acting as the carrier in a solid dispersion contributes to the solubility and dissolution rates of drugs, the reduction of particle size, the improvement of wettability, the amorphous conversion of crystalline drugs, and physical stability [11]. In this study, we examined differences in solubility improvement in spray-dried solid dispersions of nifedipine, a poorly soluble drug, prepared using various polymers and, as an indirect indicator of drug bioavailability, comparative dissolution experiments were performed.

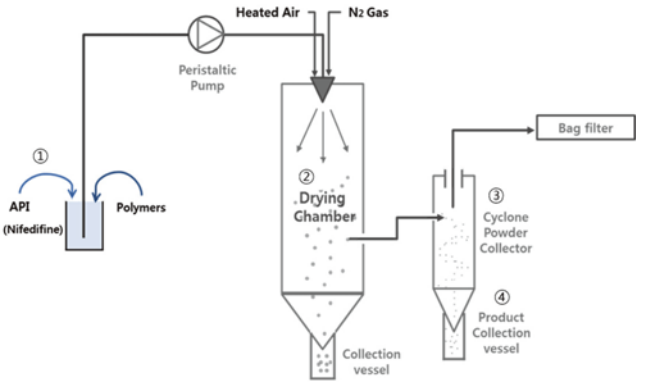

Fig. 1. Scheme of the spray-drying manufacturing method: Feed ①, Spray-drying chamber ②, Separating ③, and Spray-dried product ④.

Table 1. Spray-drying conditions

Parameter	Setting
Inlet temperature	80~90°C
Outlet temperature	60~65°C
Spray nozzle diameter	1.2 mm
Feed rate	6 mL/min

2. Materials and Methods

2.1. Reagents and materials

Nifedipine, the study's low solubility drug, was purchased from Xilin Pharma (China). The HPMC, hypromellose phthalate (HPMCP), and hypromellose acetate succinate (HPMCAS) polymers were purchased from Lotte Fine Chemical (Korea). The povidone K-30 (PVP K-30) was produced by Ashland (USA), and the Eudragit (Eudragit E100, L100, L100-55) polymethacrylate-based copolymer was obtained from Degussa (Korea).

2.2. Solid dispersion preparation

The PVP K-30, HPMC, HPMCP, HPMCAS, and Eudragit polymers were separately mixed (1:1) with nifedipine and dissolved in a mixed solvent of ethanol/methylene chloride (2:8), followed by processing in a spray dryer (Mini Spray Dryer B-290, Büchi Labortechnik AG, Flawil, Switzerland) to form solid dispersions. The solid dispersion manufacturing method is schematically shown in Fig. 1. The nifedipine (active pharmaceutical ingredient, API) and polymer components comprised 3.4% of the ethanol/methylene chloride mixed solvent. The spray-drying conditions are summarized in Table 1.

2.3. Morphological characterization of solid dispersions

To observe the particle state and surface characteristics of the spray-dried solid dispersions, they were examined using a scanning electron microscope (SEM; Mini SEM, SNE-3000M, SEC, Korea). In preparation for SEM analysis, samples were fixed on carbon tape and platinum coated. Samples were observed at 20.0 kV.

2.4. Crystallinity analysis

Differential scanning calorimetry (DSC; 204 F1 Phoenix, NETZSCH, Wittelsbacherstraße, Germany) was undertaken to determine the thermal properties of the nifedipine solid dispersion and the polymer used. For calorimetry, a sample (2-3 mg) was placed in an aluminum pan, and the characteristic peak melting temperature was observed over the temperature range of 20-220°C and a temperature increase rate of 10°C/min. In addition, a high-resolution X-ray diffractometer (HR-XRD, Rigaku, Japan) was used to observe the crystallinity of the solid dispersion. The diffraction scan range was 5-65° and was measured using a scan increase rate of 1.8°/min.

2.5. Drug release rate measurement

To examine the possibility of solubility improvements of nifedipine solid dispersions, powder dissolution tests to compare solubilities of nifedipine raw material and solid dispersions of nifedipine were carried out by applying the paddle method described in the Korean Pharmacopoeia. Artificial intestinal fluid (pH 6.8) and artificial gastric fluid (pH 1.2) were prepared and applied according to a method

described in the Korean Pharmacopoeia. The solubilities of nifedipine and the nifedipine solid dispersions in an eluent (DT1420; ERWEKA, Heusenstamm, Germany) were measured. During dissolution testing, paddle speed was set at 50 r/min, eluent temperature at 37 ± 0.5ºC, and eluent amount was 900 mL. Sampling (5 mL) occurred at preset times, and the eluate was replenished after sampling. The collected sample was filtered through a 0.45 μm PTFE filter and subjected to high-performance liquid chromatography (HPLC). An Agilent HPLC analyzer (1200 Series, Agilent, Morges, Switzerland) was used to determine the drug release rate. A 5 μm C18 column (250 × 4.6 mm) with a 1.2 mL/min flow rate was used. The injected amount of a sample was set for a 50 μm analysis. The UV wavelength was analyzed at 254 nm. The mobile phase was mixed with acetonitrile at a ratio of 6:4 (v/v %), and the aqueous KH_2PO_4 solution was adjusted to pH 2.5 by adding phosphoric acid.

3. Results and Discussion

3.1. Morphological characteristics of solid dispersions

Scanning electron microscopy was undertaken to observe nifedipine's particle state and surface characteristics (Fig. 2). Nifedipine crystallinity observations revealed relatively large but inconsistent particles with a size range of 10 to 80 μm (Fig. 2A). The results showed that the raw nifedipine particle size was 10 fold larger than those of each of the prepared solid dispersions in which particle sizes were less than 10 μm. Fig. 2D-I reveals that the solid dispersions prepared with cellulose-based polymers had relatively consistent particle sizes with a size under 10 μm. Fig. 2J and 2K show that the Eudragit L100 and L100-55 solid dispersions had larger and more inconsistent particle sizes than those of the cellulose-based solid dispersions.

3.2. Crystallographic analysis of solid dispersions

Fig. 3 shows the crystallographic characteristics of raw nifedipine and the nifedipine solid dispersions according to polymer type as revealed by DSC. Nifedipine showed a strong endothermic peak at 171.77ºC, typical of a crystalline drug. The PVP, HPMC (6cps; AN6), HPMCP, and HPMCAS solid dispersions did not show crystalline peaks, but crystalline peaks did appear in the solid dispersions containing Eudragit (Fig. 3B). As shown in the DSC analysis results, the intrinsic crystallinity of nifedipine changed when it was incorporated in a solid dispersion with various polymers [11]. The intrinsic crystallinity of nifedipine changed to amorphous due to losing its specific crystallinity through the spray-drying process [12].

The inherent diffraction peak of nifedipine was observed at 0~30°, whereas the inherent diffraction peaks were 15~25° in the Eudragit-containing solid dispersions (Fig. 4).

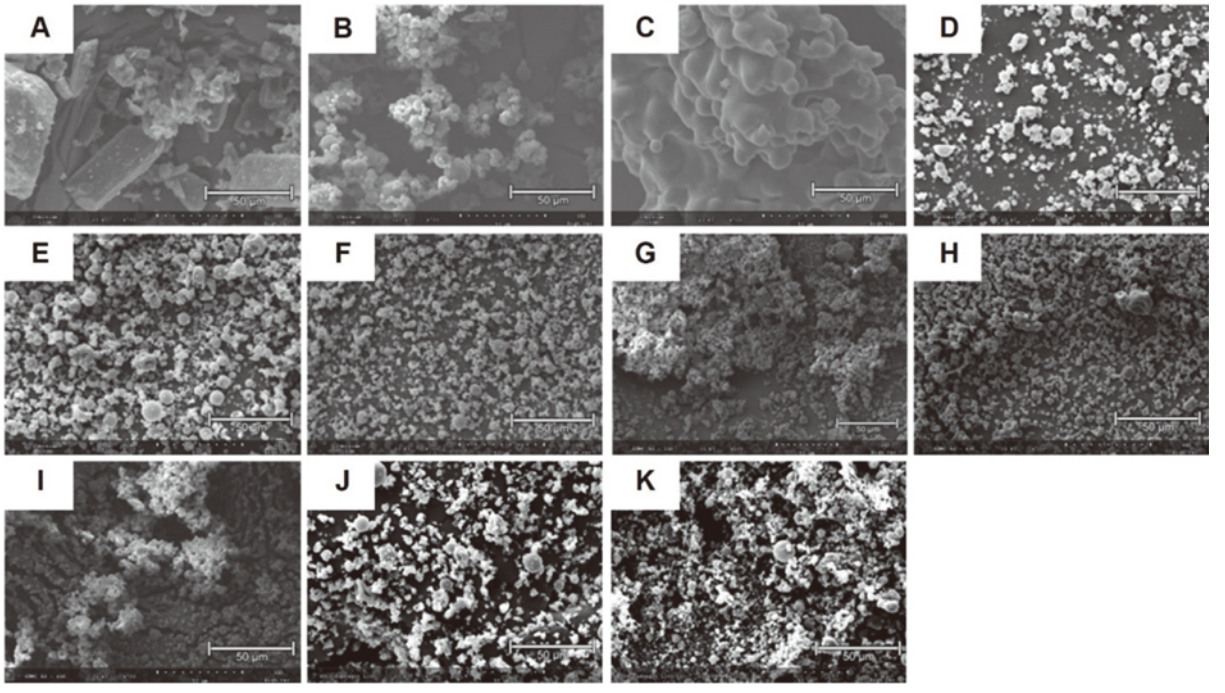

Fig. 2. Particle forms of nifedipine raw material and solid dispersions containing various polymers. (A) Nifedipine, (B) PVP, (C) Eudragit E100, (D) HPMC(6cps), (E) HPMCP-50, (F) HPMCP-55, (G) HPMC AS-55G, (H) HPMC AS-60G, (I) HPMCAS-65G, (J) Eudragit L100, and (K) Eudragit L100-55.

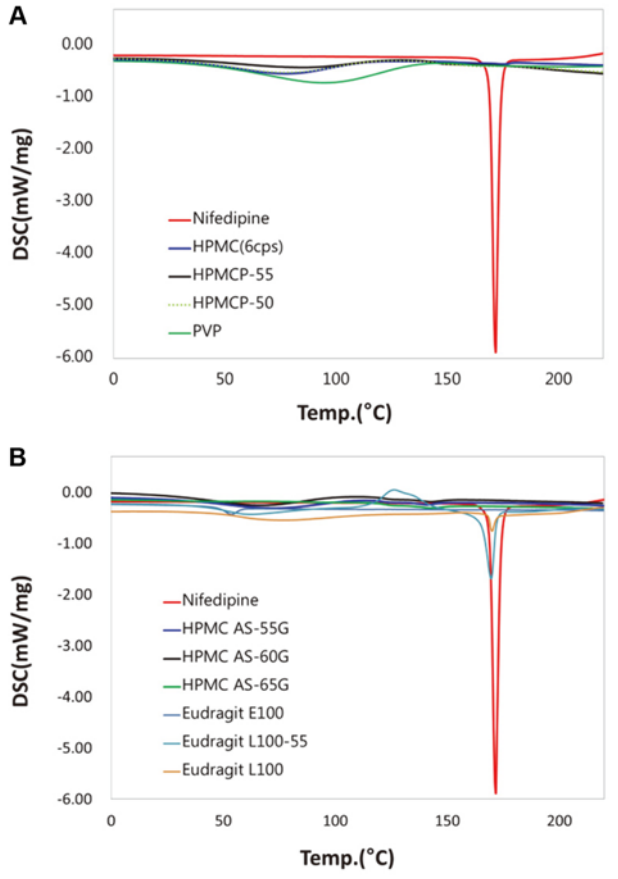

Fig. 3. Differential scanning calorimetry graphs of nifedipine and solid dispersions obtained through a spray-drying process. (A) Nifedipine (red), HPMC(6cps) (dark blue), HPMCP-55 (black), HPMCP-50 (yellow), and PVP (green). (B) Nifedipine (red), HPMCAS-55G (dark blue), HPMCAS-60G (black), HPMCAS-65G (blue), Eudragit E100 (light blue), Eudragit L100-55 (green), and Eudragit L100 (yellow).

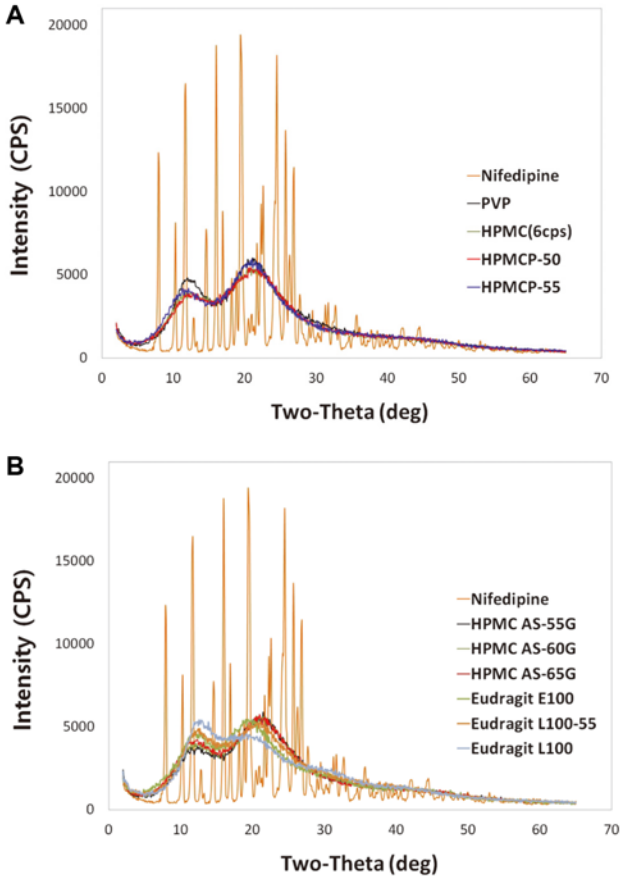

Fig. 4. X-ray diffraction graph of solid dispersions containing nifedipine raw materials and polymers. (A) Nifedipine (yellow), PVP (dark blue), HPMC(6cps) (blue), HPMCP-50 (red), and HPMCP-55 (green). (B) Nifedipine (yellow), HPMCAS-55G (dark blue), HPMCAS-60G (green), HPMCAS-65G (orange), Eudragit E100 (green), Eudragit L100-55 (light orange), and Eudragit L100 (light blue).

However, in the HPMC-containing solid dispersions and the PVP-containing solid dispersion, no distinct diffraction peaks were observed [13]. The DSC and XRD results revealed that the crystallinity of the raw nifedipine was lost when solid dispersions were prepared by spray drying of nifedipine with HPMC- and PVP-based polymers. This loss of crystallinity resulted from the drug being encapsulated in the amorphous polymer during the spray-drying process; thus, the drug's form appears to become nearly amorphous [14].

The results confirm that the surface characteristics and sizes of the solid dispersions differ according to each polymer type, suggesting that the selection of the solvent or the spray-drying method should differ when a specific polymer type is applied. That is, it is important to select a solvent that melts in a manner appropriate to the type of polymer; thus, it can be inferred that the surface and particles of the solid dispersion will vary depending on the setting of the device used in the spray-drying process [15]. Further testing is needed to confirm these suggestions.

3.3. Drug release behavior of nifedipine

Fig. 5 shows the results of dissolution tests in artificial gastric juice and intestinal fluid using the original nifedipine drug and the solid dispersion powders containing various polymers. The raw nifedipine drug had a less than 10% drug release rate in both gastric and intestinal fluids. Incorporation of nifedipine in the enteric polymers HPMCP, HPMCAS, and Eudragit L100 (dissolution above pH 6.0) produced low nifedipine release rates in gastric juice, but the dissolution rates increased by more than 30% in artificial gastric juice. In particular, compared to the nifedipine release rate, the solid dispersions containing HPMCP-55 and HPMCAS-60G produced approximately 10 times higher drug release rates in the artificial intestinal fluid. It appears that the pH-dependent solubility of

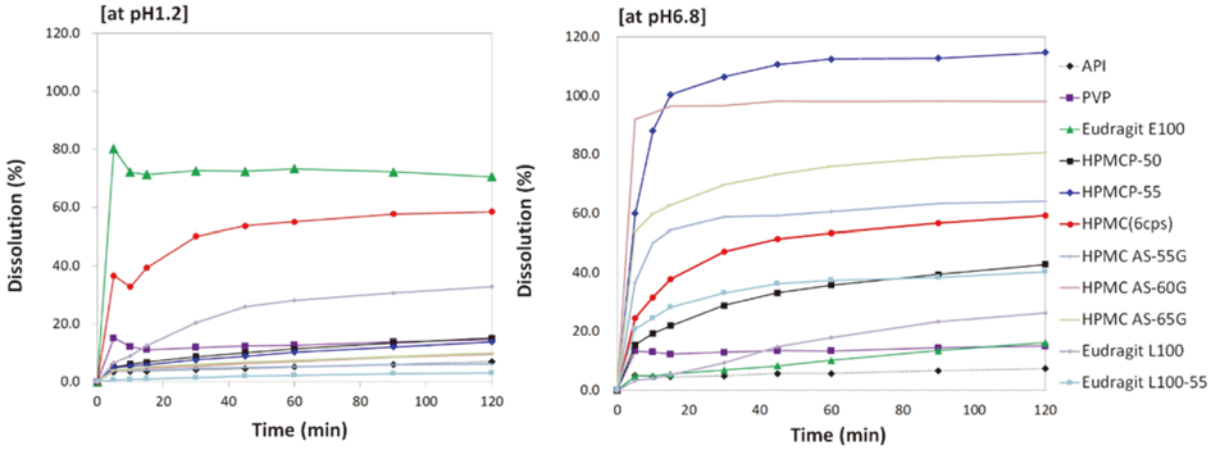

Fig. 5. Drug release rate of nifedipine raw material and polymer-containing solid dispersions. Graph shows dissolution results for nifedipine raw material and solid dispersions containing various polymers in artificial gastric juice and intestinal fluid at pH 1.2 (A) and pH 6.8 (B), respectively. Nifedipine (blue circle), PVP (black square), HPMCP-50 (dark blue square), HPMCP-55 (light blue circle), HPMC(6cps) (red circle), HPMCAS-55G (light blue), HPMCAS-60G (orange), HPMCAS-65G (green), Eudragit E100 (green triangle), Eudragit L100 (purple triangle), and Eudragit L100-55 (light blue triangle).

HPMCP-55 (insoluble at pH lower than 5.5) and HPMCAS-60G (soluble at pH 6.0, granule type) results in faster dissolution under enteric conditions compared to that of the other polymers, thereby affecting the drug release rate. Solid dispersions containing HPMC-based polymers showed higher drug release rates compared to PVP- and Eudragit-based polymers in both artificial gastric and artificial intestinal juices. Thus, a solid dispersion with a HPMC-based polymer can incorporated drugs more efficiently than solid dispersions using other polymers, with that efficiency improvement the result of the dispersion's ability to inhibit the aggregation of the drug during release. It is believed that the spray-drying method for drug product manufacture applied in this study is particularly effective when cellulose-based polymers are used, with the results indicating that the raw material of nifedipine can be well bonded to a cellulose polymer [14-16].

4. Conclusion

In this study, differences in solubility and crystallographic characteristics were compared according to the types of polymers used in preparing solid dispersions to improve the solubility of nifedipine, a poorly soluble drug. The results showed that the solubility of each solid dispersion was improved compared to that of raw nifedipine; moreover, all of the prepared solid dispersions were morphologically similar to an amorphous form. All solid dispersions were prepared using a consistent application of the solvent and the spray-drying process. Based on the spray-drying method applied, HPMCP-55 significantly increased the solubility of nifedipine under enteric conditions. In the solid dispersions that incorporated cellulose-based polymers, the solubility of nifedipine was higher than that of the other polymers. The main factors affecting drug solubilization in a solid dispersion appear to be particle size, crystalline form, drug aggregation prevention, and solubilizer selection. If these factors are appropriately considered, a relatively high drug release rate can be achieved compared to that of the raw nifedipine. However, in order to attain drug-specific appropriate physical characteristics, the solid dispersion production method should be optimized.

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Ethical Statements

The authors declare no conflict of interest.
Neither ethical approval nor informed consent was required for this study.

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