Comparison of Nicotinamide, Ethylurea and Polyethylene Glycol as Carriers for Nifedipine Solid Dispersion Systems

Hideshi SUZUKI^{*,a} and Hisakazu SUNADA^b

Fuji Laboratory, Janssen-Kyowa Co., Ltd.,^a 600-8 Minami-isshiki, Nagaizumi-cho, Sunto-gun, Shizuoka 411, Japan and Faculty of Pharmacy, Meijo University,^b 150, Yagotoyama, Tempaku-ku, Nagoya 468, Japan.

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The most prevalent means for producing solid dispersions of nifedipine, a poorly water-soluble drug, are the solvent based processes that bring problems of environmental and health. We have investigated the preparation of solid dispersions of nifedipine (mp 173 °C) by the fusion method, using nicotinamide, ethylurea, polyethylene glycol (PEG) 6000 and hydroxypropylmethylcellulose (HPMC) as carriers. All these solid dispersions were obtained by cooling at room temperature after heating at 140 °C for 15 min. As a single carrier, nicotinamide, ethylurea and PEG were used because nifedipine dissolved in their fused liquids. Compared with the physical mixtures, the solid dispersions with ethylurea or PEG led to a higher dissolution rate of the drug, whereas the difference in drug release between the physical mixtures and the solid dispersions with nicotinamide was not clear. This peculiarity might be due to the high solubilizing effect of nicotinamide for the drug. The fused mixtures of nicotinamide-, ethylurea- or PEG-HPMC were utilized as combined carriers. HPMC dissolved in the fused liquids of nicotinamide or ethylurea, which was effective in forming the amorphous nifedipine in solid dispersions. This resulted in not only the enhanced dissolution rate but also the supersaturation behavior of nifedipine. Further, for the nicotinamide-HPMC system, the supersaturation level of nifedipine increased with an increase in the HPMC content of solid dispersions. Nicotinamide was more applicable than ethylurea and PEG for preparation of the fused dispersions of nifedipine.

Key words nifedipine; solid dispersion; combined water-soluble carrier; nicotinamide; hydroxypropylmethylcellulose

It is well established that the rate-determining step in the absorption process for poorly water-soluble drugs is the dissolution rate of such drugs in the gastrointestinal fluids rather than the rapidity of their diffusion across the gut wall. The formation of solid dispersion of the drug with an inert water-soluble carrier is one of several techniques that can be used to improve the drug dissolution properties, and consequently, numerous attempts have been reported for over thirty years.^{1,2)} Broadly speaking, there are two methods of preparing solid dispersions: namely by fusion or solvent processes. Problems with solvent based processes involving both environmental concerns with solvent emissions and health concerns with residual solvent are being given careful consideration,³⁾ and are calling for alternative ways of production. The fusion method without organic solvents has thus become increasingly important. However, use of the fusion method may itself lead to undesirable processing properties caused by tacky or glassy solids⁴⁾; devitrification of tacky or glassy dispersions or their pulverization may induce crystallization and modify their dissolution characteristics.⁵⁾ In the past, novel techniques have permitted formulation into elegant dosage forms.^{6,7)}

Nifedipine, a calcium-channel agent, is a useful drug in the treatment of a variety of cardiovascular disorders including angina pectoris and hypertension.^{8,9)} It is a poorly water-soluble drug, whose bioavailability is low when orally administered in crystalline form.¹⁰⁾ For rapid dissolution, solid dispersions of nifedipine with the water-soluble carriers urea,¹¹⁾ polyethylene glycol (PEG),¹²⁾ sucrose ester,¹³⁾ polyvinylpyrrolidone (PVP),¹⁰⁾ and hydroxypropylmethylcellulose (HPMC)¹⁴⁾ have been developed. Nevertheless, many of the solid dispersions have been produced by the solvent removal processes, and thus far carriers other than PEG have hardly been used for the

fused dispersions of the drug.

The aims of this study were, firstly, to present the dissolution profiles of nifedipine from solid dispersions prepared by the fusion method using three different water-soluble carriers: nicotinamide, ethylurea and PEG; and, secondly, to examine the feasibility of solubility enhancement of the drug by preparing solid dispersions with both the above carrier and HPMC as combined carriers.

Experimental

Materials Nifedipine, nicotinamide, urea, ethylurea and PEG were obtained from Wako Pure Chemical Industries Co., Ltd., Japan. Xylitol (Towa Chemical Industries Co., Ltd., Japan), erythritol (Nikken Chemicals Co., Ltd., Japan) and HPMC (TC-5E, Shin-Etsu Chemical Industries Co., Ltd., Japan) were used. All other chemicals were of reagent grade. All experiments were carried out under subdued light to prevent light degradation of nifedipine.

Preparation of Solid Dispersion Systems The physical mixtures were prepared by grinding together accurately weighed quantities of nifedipine and an excipient using a mortar and pestle for 1—2 min. Solid dispersions of nifedipine (1 g) and nicotinamide, ethylurea or PEG (3—10 g) with or without HPMC (1—3 g) were obtained by the fusion process, that is, by fusing the corresponding physical mixtures on a hot-plate at 140 ± 5 °C for 15 min. The surface temperature of six points on the hot-plate was measured by an infrared thermometer (COS Co., Ltd., Japan).

The fused samples were cooled at room temperature and solidified by placing them for 1—5 d in a desiccator over silica gel before pulverizing them in a coffee mill. In all experiments, the fused dispersions were sieved through 42 mesh and assayed for their drug content before use by HPLC at 237 nm.

Drug Solubility Studies Excess amounts of nifedipine were added to aqueous solutions (5 ml) containing various concentrations of nicotinamide, ethylurea or PEG. After shaking for 48 h at 37 °C, samples were withdrawn, filtered (0.2 µm), diluted and analyzed by HPLC at 237 nm.

Drug Solubility Assay Aliquots obtained by filtration were appropriately diluted with methanol and assayed at 237 nm by HPLC. The chromatograph operating conditions were as follows: C18 reversed-phase column (YMC-Pack ODS-H80); 0.05 M phosphate buffer (pH 3.0); methanol: tetrahydrofuran (60:32:8) eluant; flow rate of 1.3 ml/min; 237 nm detector (Shimadzu Seisakusho Co., Ltd., Japan).

* To whom correspondence should be addressed.

Dissolution Studies Dissolution tests according to JP XIII (paddle method, 100 rpm) were carried out at 37°C. A weighed quantity of physical mixture or solid dispersion containing 80 mg of nifedipine was placed in 900 ml of distilled water. Samples were filtered (0.2 μ m) and assayed by HPLC at 237 nm.

Differential Scanning Calorimetry (DSC) DSC analyses for the solubility potential of nifedipine in the fused excipients were carried out on samples of 5 to 10 mg on a DSC 220CU (Seiko Denshi Kogyo Co., Ltd., Japan). Samples were heated at a rate of 10°C/min to 190°C in nitrogen. Melting point (mp) was characterized by the temperature at the point of intersection of the steepest slope line and the baseline.

Powder X-Ray Diffraction Analysis Powder X-ray diffraction analyses were performed with a Rigaku Geiger-Flex diffractometer (Rad-IIVC) using Ni-filtered, CuK α radiation, a voltage of 40 kV and a current of 20 mA. The scanning rate was 5°/min over a 2 θ range of 2–50° and with a sampling interval of 0.02°.

Phase Diagram Determination A number of accurately weighed binary mixtures of nifedipine–nicotinamide, –ethylurea or –PEG systems and of nicotinamide– or ethylurea–HPMC systems of various compositions, were heated using a capillary melting point apparatus (B-530, Shibata Scientific Technology, Ltd., Japan). A sample was placed in a glass capillary tube and heated at a rate of 3°C/min. Visualization was possible using a high-powered magnifying glass fixed on a mount over the sample. All determinations were made in triplicate. For the purpose of constructing phase diagrams, observations were made noting the temperature at which melting started (thaw point) and the temperature at which complete melting was accomplished (melting point). These temperatures were used to describe the solidus and liquidus lines.

Polymer Compatibility Studies The physical mixture of 3:1 weight ratio of nicotinamide, ethylurea or PEG:HPMC was heated using the capillary melting point apparatus at a rate of 3°C/min. Visual observations were made noting the temperature at which complete melting was accomplished.

Results and Discussion

Selection of Suitable Carriers Suitable carriers for preparing nifedipine solid dispersions by the fusion method were selected by testing the solubility and miscibility of nifedipine in the liquid state of six easily water-soluble and inert excipients (Table 1). All have a lower melting point than nifedipine (mp 173°C), which is convenient to avoid drug decomposition for excessive heat during the preparation of dispersions if the drug is soluble in the fused liquids. DSC thermograms on the physical mixtures of nifedipine with each excipient (1:3 weight ratio of drug:excipient) were determined up to 190°C. For the physical mixtures of nifedipine with urea, xylitol or erythritol, two endothermic peaks corresponding to the melting of nifedipine and the excipient were recognized. In contrast, for the physical mixtures of nifedipine with nicotinamide, ethylurea or PEG, the endothermic peak corresponding to the melting of nifedipine almost disappeared. It was thus evident that the drug was more soluble in the fused liquids of nicotinamide, ethylurea and PEG.

Table 1. Melting Points of Nifedipine and Excipients

		mp (°C)
Drug	Nifedipine	173
Excipient	Nicotinamide	129
	Urea	135
	Ethylurea	90
	Xylitol	93
	Erythritol	119
	PEG6000	60

The data were measured by DSC.

Moreover, using the same physical mixtures, the miscibility in the fused mixtures of nifedipine and excipients was evaluated on the hot plate. When the physical mixtures of nifedipine and urea, xylitol or erythritol fused at about 180°C, the drug and excipient in the liquid state were not completely miscible. These combinations belong to the classification “insoluble-immiscible” described by Kanig,¹⁵ suggesting that these three excipients are not appropriate to utilize as carriers for preparing nifedipine solid dispersions by the fusion method. On the contrary, when the physical mixtures of nifedipine and nicotinamide, ethylurea or PEG fused at about 140°C, the drug dissolved in the fused excipient, and the two components were entirely miscible. Thereafter, in the cooling process under room temperature, these systems solidified into a discernible solid by complete crystallization which might maintain the drug as a fine crystalline dispersion. Consequently, in the following experiments, nicotinamide, ethylurea and PEG were used as carriers for preparing fused dispersions of nifedipine.

The phase diagrams for the physical mixtures of nifedipine–nicotinamide, –ethylurea or –PEG are shown in Fig. 1. The liquidus point for nifedipine–ethylurea or –PEG systems increased with an increase in the proportion of nifedipine (Fig. 1, B, C). The slope of the liquidus line for the nifedipine–PEG system was higher than that for the nifedipine–ethylurea system. These phase diagrams were characterized by the absence of complete dissolution of nifedipine in the fused liquids of ethylurea and PEG at their melting points. That is to say, the rising liquidus lines were viewed as corresponding with the drug solubility in the fused carriers at a specified temperature.¹⁶ The phase diagram of the nifedipine–nicotinamide system, however, depicted a simple eutectic type (Fig. 1, A); the eutectic composition of this system was found to be 25% w/w of nifedipine and 75% w/w of nicotinamide (1:3 weight ratio of drug:nicotinamide), and its temperature was 124°C. The rapid solidification of the fused mixture at this ratio might produce a eutectic mixture. It must further be emphasized that the fused liquid with nicotinamide that contains less than 40% w/w of nifedipine can be obtained

Fig. 1. Phase Diagrams of Nifedipine Physical Mixtures with Nicotinamide, Ethylurea or PEG6000

A, nifedipine–nicotinamide; B, nifedipine–ethylurea; C, nifedipine–PEG6000. Solid line, liquidus line; dashed line, solidus line.

at a temperature below the melting point of nicotinamide itself. However, to dissolve the same amount of nifedipine in the fused liquids of ethylurea or PEG, a much higher temperature than the intrinsic melting point of the carrier was required. This implied that nicotinamide was more suitable than ethylurea and PEG as a carrier of the fused dispersions in suppressing of thermal degradation and sublimation.

Solubility Studies Equilibrium solubility studies at 37°C were conducted to estimate the solubilizing effects of nicotinamide, ethylurea and PEG for nifedipine (Fig. 2). Nicotinamide was found to interact strongly with nifedipine in aqueous solution. Over the concentration range of nicotinamide, a 6.8-fold increase in the solubility of nifedipine was seen; the drug solubility was 9.3 µg/ml intrinsically, and reached 63.5 µg/ml in 4.0% w/v of nicotinamide solution. Nicotinamide is well known as a hydrotropic agent, and its ability to solubilize a wide variety of therapeutic compounds has been demonstrated.¹⁷⁾ The term "hydrotropy" refers to a solubilization process whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of a sparingly soluble solute, and positive deviation of the solubility curve is characteristic of hydrotropic solubilization.¹⁸⁾ However, the exact mechanism by which nicotinamide forms complexes has not been thoroughly examined. Concerning ethylurea and PEG, the solubilization of nifedipine was found to be linear, but it was weaker than nicotinamide, resulting in about 2-fold solubility of the drug over the concentration range studied. Since ethylurea and PEG have amino or hydroxyl groups and hydrophobic groups, it is possible that both the interference with the water structure and the formation of hydrophobic interactions contribute to the solubilization of the drug.^{19,20)}

The studies by Jafari *et al.*²¹⁾ show that for the solid dispersions of miconazole nitrate containing high concentration of a carrier, the contribution of wetting and solubilizing ability of the carrier is more important than the reduction of drug particle size resulted from the formation of a eutectic mixture. From the strong solubilizing effect of nicotinamide, it is reasonable to assume that forming a eutectic mixture of nifedipine–nicotinamide

Fig. 2. Effect of Carriers on Aqueous Solubility of Nifedipine at 37°C
●, nicotinamide; ▲, ethylurea; ■, PEG6000.

(1:3 weight ratio of drug:nicotinamide) may be a less effective means of improving the drug dissolution rate than increasing the proportion of nicotinamide in the solid dispersion. Furthermore, even for solid dispersions with ethylurea or PEG that form no eutectic mixture, the increase in carrier content may contribute to the improvement of the drug dissolution rate. Therefore, the following studies for solid dispersions with a single carrier were conducted using a 1:5 weight ratio of drug:carrier.

Dissolution Profiles of Solid Dispersions with a Single Carrier The dissolution profiles of nifedipine solid dispersions with nicotinamide, ethylurea or PEG and their physical mixtures of 1:5 weight ratio of drug:carrier are shown in Fig. 3. It was obvious that the dissolution rate of nifedipine from the solid dispersions with ethylurea or PEG was much higher than that from the physical mixtures, which is a general phenomenon in the studies on solid dispersions. However, interestingly, the rapid dissolution of nifedipine from the physical mixture with nicotinamide was an unexpected observation; it was equivalent to the dissolution rate of the solid dispersions with nicotinamide or ethylurea, and was superior to that of the other physical mixtures.

To clarify this peculiarity, dissolution tests were done increasing the proportion of nicotinamide in both the physical mixtures and the solid dispersions (Fig. 4). Although the lower content of nifedipine resulted in faster dissolution rate, no difference was noticed in the drug dissolution profiles between the physical mixtures and the solid dispersions. Figure 5 represents the X-ray diffraction patterns of physical mixture and solid dispersion samples. Peaks of 7.9, 10.3 and 11.7° 2θ in the crystalline nifedipine were detected for each sample. The heights of these peaks were similar in both physical mixture and solid dispersion of the same proportion, suggesting that the entire amount of the drug exists as a pure crystalline phase in the solid dispersions. The X-ray diffraction pattern of the fused nicotinamide was somewhat different from that of untreated sample; it cannot be excluded that the solid structure of nicotinamide was slightly altered by the fusion process performed in this study. Since many carriers increase the

Fig. 3. Dissolution Profiles of Nifedipine Solid Dispersions with Nicotinamide, Ethylurea or PEG6000 (Drug:Carrier = 1:5)

+, nifedipine; ○, ●, nicotinamide; △, ▲, ethylurea; □, ■, PEG6000. Open symbols, solid dispersions; closed symbols, physical mixtures.

Fig. 4. Dissolution Profiles of Nifedipine Solid Dispersions with Nicotinamide

+, nifedipine; ○, ●, drug:carrier=1:5; △, ▲, drug:carrier=1:10. Open symbols, solid dispersions; closed symbols, physical mixtures.

Fig. 5. Powder X-Ray Diffraction Patterns of Nifedipine Solid Dispersions with Nicotinamide

A, nifedipine; B, nicotinamide; C, nicotinamide (fused sample); D, physical mixture (drug:carrier=1:5). Solid dispersions: E, drug:carrier=1:5; F, drug:carrier=1:10. The arrows mark the positions for characteristic nifedipine lines.

aqueous solubility of a drug thereby increasing the dissolution rate, it can be predicted that the higher the solubilizing effect of a carrier, the smaller the difference in the dissolution rates between physical mixture and solid dispersion. This assumption is in accordance with the findings of Hamza *et al.*²²⁾ who showed that the dissolution rate of 10% w/w indomethacin physical mixture with

Table 2. Melting Points of Physical Mixtures of Carrier and HPMC (Carrier:HPMC=3:1)

Carrier	mp (°C)
Nicotinamide	130
Ethylurea	132
PEG6000	—

The data were measured by a capillary melting point apparatus. —: HPMC was insoluble.

nicotinamide was close to that of solid dispersion prepared as a coprecipitate. Thus, a reasonable explanation for there being no difference in nifedipine dissolution profiles between the physical mixtures and the solid dispersions with nicotinamide would be the high solubilizing effect of nicotinamide.

Major peaks of nifedipine were also found in the X-ray diffraction patterns of dispersion systems with ethylurea or PEG used in Fig. 3. The increase in the drug dissolution rate from solid dispersions has generally been attributed to the reduction of drug particle size within solid dispersions.²³⁾ Moreover, since a poorly water-soluble drug with a strong hydrophobicity results in its floating on the surface of dissolution medium, it is thought that the better the wettability and dispersibility of a drug in a solid dispersion system, the better the chances of achieving an increase in drug dissolution rate.²¹⁾ Accordingly, both the size reduction of the drug and the good wettability of solid dispersions might account for the faster dissolution rate of nifedipine-ethylurea or -PEG dispersions than that of the physical mixtures (Fig. 3).

Solubility Enhancement of Solid Dispersions with Combined Carriers Nifedipine solid dispersions with a single carrier improved the drug dissolution rate, but there was not a marked increase in the drug solubility. This may be because nifedipine in fused dispersions was present in an almost entirely crystalline state. So attempts were made to enhance the aqueous solubility of nifedipine by preparing fused dispersions with nicotinamide-, ethylurea- or PEG-HPMC as combined carriers. The reason for the use of HPMC as a second carrier is the strong possibility that the polymer inhibits the crystallization of nifedipine in preparation and dissolution; the results of Sugimoto *et al.*¹⁴⁾ indicate that nifedipine in solid dispersions with HPMC prepared by the solvent method exists in the amorphous form, thereby inducing not only a supersaturation phenomenon but also good bioavailability of the drug.

The compatibility of HPMC was initially confirmed by heating the physical mixtures of 3:1 weight ratio of nicotinamide, ethylurea or PEG:HPMC (Table 2). Thermal characteristics of HPMC that is essentially amorphous have been reported to be a glass transition at 150–165°C and a transition of thermal degradation around 223°C.²⁴⁾ In the fused liquids of nicotinamide or ethylurea, HPMC appeared completely soluble at a lower temperature than the glass transition point of the polymer, but did not dissolve in PEG even when heated up to about 230°C. Figure 6 shows phase diagrams for the physical mixtures of nicotinamide- or ethylurea-HPMC. The solubility of HPMC in the liquid state of nicotinamide

Fig. 6. Phase Diagrams of Nicotinamide or Ethylurea Physical Mixtures with HPMC

A, nicotinamide-HPMC; B, ethylurea-HPMC. Solid line, liquidus line; dashed line, solidus line.

Fig. 7. Dissolution Profiles of Nifedipine Solid Dispersions with Nicotinamide, Ethylurea or PEG6000 and HPMC (Drug: Carrier: HPMC = 1:3:1)

+, nifedipine; ○, ●, nicotinamide; △, ethylurea; □, PEG6000. Open symbols, solid dispersions; closed symbol, physical mixture.

was higher than that in ethylurea; the fused nicotinamide at the intrinsic melting point dissolved about 30% w/w of the polymer, but when the same amount of the polymer dissolved in the fused liquid of ethylurea, the heating temperature rose to almost 140°C, 50°C higher than the melting point of ethylurea itself. These results indicated that HPMC had higher compatibility with nicotinamide than ethylurea.

The dissolution profiles of nifedipine solid dispersions with combined carriers (1:3:1 weight ratio of drug: nicotinamide, ethylurea or PEG: HPMC) are presented in Fig. 7. Nifedipine solid dispersions with nicotinamide- or ethylurea-HPMC brought about a remarkable increase in not only the dissolution rate but also the solubility of the drug. On the contrary, for the solid dispersion with PEG-HPMC, the enhanced solubility of nifedipine was not observed, and it was approximately equal to the physical mixture with nicotinamide-HPMC. The concentrations of nifedipine after 45 min for the solid dispersions with nicotinamide-, ethylurea- and PEG-HPMC were 37.1, 34.3 and 10.4 µg/ml, corresponding to 4.0, 3.7 and 1.1-

Fig. 8. Powder X-Ray Diffraction Patterns of Nifedipine Solid Dispersions with Nicotinamide, Ethylurea or PEG6000 and HPMC (Drug: Carrier: HPMC = 1:3:1)

A, nifedipine; B, nicotinamide (fused sample); C, ethylurea; D, PEG6000; E, HPMC. Solid dispersions: F, nicotinamide-HPMC; G, ethylurea-HPMC; H, PEG6000-HPMC. The arrows mark the positions for characteristic nifedipine lines.

fold increase in the intrinsic drug solubility, respectively. The X-ray diffraction patterns of the solid dispersions with nicotinamide- or ethylurea-HPMC were quite different from that of the solid dispersion with PEG-HPMC (Fig. 8): the major X-ray diffraction peaks of nifedipine disappeared, and the intensity values of nicotinamide and ethylurea were considerably lower. These results implied that nifedipine was present as an amorphous state, and the crystallinity of nicotinamide and ethylurea was greatly decreased. However, these results were not found in the solid dispersion with PEG-HPMC. Consequently, it can be presumed that the dissolved HPMC in the fused liquids of nicotinamide or ethylurea acts effectively to inhibit nifedipine crystallization during the cooling process, thereby leading to the supersaturation phenomenon in the dissolution studies (Fig. 7).

Further evidence of the HPMC effect on the solubility of nifedipine was obtained in the dissolution tests of the solid dispersions with from 1:3:1 to 1:3:3 weight ratio

Fig. 9. Dissolution Profiles of Nifedipine Solid Dispersions with Nicotinamide or Ethylurea and HPMC

+, nifedipine; ○, ●, drug:carrier:HPMC=1:3:1; △, ▲, drug:carrier:HPMC=1:3:2; □, ■, drug:carrier:HPMC=1:3:3. Open symbols, solid dispersions with ethylurea and HPMC; closed symbols, solid dispersions with nicotinamide and HPMC.

of drug:nicotinamide or ethylurea:HPMC (Fig. 9). The concentration of nifedipine for the solid dispersions with nicotinamide-HPMC increased with an increase in the polymer content, but the difference in drug concentration between two dispersions at 1:3:2 and 1:3:3 was less than that at 1:3:1 and 1:3:2. For the solid dispersions with ethylurea-HPMC, on the other hand, there was no obvious enhancement of the drug concentration proportional to the polymer content. Accordingly, the HPMC effect on the nifedipine solubility might be definitely weakened at 3:2—3 and 3:1—2 weight ratios of nicotinamide:HPMC and ethylurea:HPMC, respectively. Converted into the proportion of HPMC, these boundary weight ratios would be about 45 and 30% w/w estimated as the dissolved proportions of HPMC when the physical mixtures of nicotinamide-HPMC and ethylurea-HPMC fused at 140°C, respectively (Fig 6). In view of these results, it followed that the dissolved amount of HPMC in the fused liquids of nicotinamide or ethylurea would have a close relation to the supersaturation level of nifedipine released from solid dispersions. Possibly this is because the dispersibility of the drug molecules in the polymer matrix increased. Also, on the 1:3:1 weight ratio of drug:carrier:HPMC, the nifedipine solubility of solid dispersion with nicotinamide-HPMC was somewhat higher than that with ethylurea-HPMC; this could result from the higher compatibility of the polymer in the fused liquid of nicotinamide than ethylurea. Nicotinamide is considered more suitable than ethylurea as a carrier of the fused dispersion for the following reasons: 1) high

solubilizing effect for nifedipine; 2) good compatibility with both nifedipine and HPMC in the fused state; 3) lower sublimation at the temperature used in the fusion method; and 4) a nontoxic vitamin.

In conclusion, the preparation of nifedipine solid dispersions by the fusion method has been examined with a single carrier and combined carriers. Nicotinamide, ethylurea and PEG were available as a single carrier, leading to an increase in the dissolution rate of nifedipine. In addition, HPMC dissolved in the fused liquids of nicotinamide or ethylurea, which were utilized as combined carriers to form the amorphous nifedipine in the solid dispersions. The use of these combined carriers resulted in not only the enhanced dissolution rate but also the supersaturation behavior of the drug. Considering the compatibility with nifedipine and HPMC, nicotinamide was more applicable than ethylurea and PEG for preparation of the fused dispersions.

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