Preparation and Evaluation of Solid Dispersion Tablets by a Simple and Manufacturable Wet Granulation Method Using Porous Calcium Silicate

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The aim of this study was to prepare and evaluate solid dispersion tablets containing a poorly water-soluble drug using porous calcium silicate (PCS) by a wet granulation method. Nifedipine (NIF) was used as the model poorly water-soluble drug. Solid dispersion tablets were prepared with the wet granulation method using ethanol and water by a high-speed mixer granulator. The binder and disintegrant were selected from 7 and 4 candidates, respectively. The dissolution test was conducted using the JP 16 paddle method. The oral absorption of NIF was studied in fasted rats. Xylitol and crospovidone were selected as the binder and disintegrant, respectively. The dissolution rates of NIF from solid dispersion formulations were markedly enhanced compared with NIF powder and physical mixtures. Powder X-ray diffraction (PXRD) confirmed the reduced crystallinity of NIF in the solid dispersion formulations. Fourier transform infrared (FT-IR) showed the physical interaction between NIF and PCS in the solid dispersion formulations. NIF is present in an amorphous state in granules prepared by the wet granulation method using water. The area under the plasma concentration–time curve (AUC) and peak concentration (C_{max}) values of NIF after dosing rats with the solid dispersion granules were significantly greater than those after dosing with NIF powder. The solid dispersion formulations of NIF prepared with PCS using the wet granulation method exhibited accelerated dissolution rates and superior oral bioavailability. This method is very simple, and may be applicable to the development of other poorly water-soluble drugs.

Key words poorly water-soluble drug; porous calcium silicate (PCS); wet granulation method; dissolution; surface solid dispersion; high-speed mixer granulator

The ‘Biopharmaceutics Classification System’ (BCS) is a very important key word in the research and development of oral formulations. The BCS classifies drugs into four classes depending on the solubility and membrane permeability of the drug. Most oral formulations show drug efficacy by first dissolving in the digestive tract then being absorbed through the membrane of the small intestine, thus entering the circulation. Oral formulations have been developed using various strategies depending on the drug’s BCS class, solubility, and membrane permeability. It was recently estimated that between 40 and 70% of all new chemical entities identified in drug discovery programs are insufficiently soluble in aqueous media.1–3) The increase in the proportion of poorly soluble candidates is frequently attributed to improvements in synthesis technology, which has enabled the design of very complicated compounds, and a change in discovery strategy from the so-called phenotypic approach to a target-based approach.4,5) Thus, the design of oral formulations to allow the rapid dissolution of poorly water-soluble drugs is important.

Solid dispersion (including amorphous) is one useful method for improving dissolution and has been investigated as a manufacturing method for solid preparations. The amorphous state has a higher Gibbs free energy than the crystalline state, and as a result has higher apparent solubility and exhibits faster dissolution rates. This in turn can lead to higher bioavailability of drugs that exhibit dissolution rate-limited absorption (classified according to the BSC as class II drugs). However, due to the high entropy, enthalpy, and free energy that give rise to this better solubility, the amorphous state is inherently unstable and recrystallization may occur.6–8) A solid drug dispersion is generally prepared by dispersion in a water-soluble carrier such as polyvinylpyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC), but these solid dispersions easily re-crystallize in the presence of moisture.9–12) Also, Konno and Taylor reported that absorbed moisture disrupts drug-PVP interactions and that this disruption persists even after the moisture is removed.11) Thus, solid dispersions are prepared under dry conditions to minimize re-crystallization.

The preparation of surface solid dispersions has been reported recently.13–20) Unlike conventional solid dispersions, the carriers used in surface solid dispersions are water-insoluble and porous materials. Planinsek et al. reported that the addition of water to a solid dispersion results in desorption of the drug from the carrier’s surface due to stronger interactions between the carrier and water than those between the carrier and the drug.16) Singh and Pathak proposed that hydrogen bond replacement underlies the mechanism of action for surface solid dispersion.17) Solid dispersions prepared using these porous materials exhibit good stability towards moisture.15,18,19) The solid dispersions described in these previous reports were generally prepared using methods that excluded water, such as melt-adsorbed and spray drying, or solution-adsorbed methods.

The structure of porous calcium silicate (PCS) resembles that of assembled petal-like flakes, has many surface pores, and can absorb a very large amount of oil (4–6 mL/g) through these pores. Solid dispersions using PCS effectively improve the dissolution of poorly water-soluble drugs.13–15) However, PCS has a low density and easily becomes airborne during
manufacturing processes, making it difficult to use in the manufacture of drug tablets. Efficient formulation processes thus require the use of higher density granular PCS. Hirai et al. reported such a granule with PCS, using sugars contained in Chinese herbal medicine by the wet granulation method. The wet granulation method is widely used in the pharmaceutical industry, and granules prepared using this method are amenable to tableting in large-scale production. However, the effect of PCS granulation by the wet granulation method on the solid dispersion of poorly water-soluble drugs is not well understood. Furthermore, little has been reported to make high density of PCS granules. Thus, the aim of the present study was to prepare and evaluate solid dispersion formulations containing nifedipine (NIF) as a model poorly water-soluble drug using PCS and a simple manufacturing wet granulation method. Granulation was performed using a high-speed mixer granulator, used extensively in the pharmaceutical industry for wet granulation, and preparation of tablet was performed using a rotary tableting machine, possible to efficiently produce. We also estimated the bioavailability of NIF following oral administration of the solid dispersion formulation to rats.

**Experimental**

**Materials** NIF was purchased from Permachem Asia Ltd. (Tokyo, Japan; purity over 99.0% (w/w)). Porous calcium silicate (Florite® RE) was kindly provided by Tomita Pharmaceutical Co., Ltd. (Tokushima, Japan). Dextrin, lactose, sorbitol, glucose, fructose, and xylitol, used as binders, were obtained from Nippon Starch Chemical Co., Ltd. (Osaka, Japan), Hayashibara Co., Ltd. (Okayama, Japan), MEGGLE GmbH. (Wasserburg, Germany), Mitsubishi Shoji Foodtech Co., Ltd. (Tokyo, Japan), Nacalai Tesque Ltd. (Kyoto, Japan), and B Food Science Co., Ltd. (Tokyo, Japan). Dextrin, trehalose, lactose, silicified microcrystalline cellulose (Prosolv SMCC90®), BASF Co., Ltd., Ludwigshafen, Germany), croscarmellose sodium (Ac-Di-Sol®, FMC BioPolymer, Philadelphia, PA, U.S.A.) and sodium starch glycophate (EXPLOTAB®, JRS PHARMA GMBH & Co., KG, Rosenburg, Germany) were used as disintegrants. Silicified microcrystalline cellulose (Prosolv SMCC90®) and magnesium stearate were obtained from JRS PHARMA GMBH & Co., KG and Nacalai Tesque Ltd., respectively. Crospovidone (Kollidon CL®, BASF Co., Ltd., Ludwigshafen, Germany), low substituted hydroxypropyl cellulose (L-HPC, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan), croscarmellose sodium (Ac-Di-Sol®, FMC BioPolymer, Philadelphia, PA, U.S.A.) and sodium starch glycophate (EXPLOTAB®, JRS PHARMA GMBH & Co., KG, Rosenburg, Germany) were used as disintegrants. Silicified microcrystalline cellulose (Prosolv SMCC90®) and magnesium stearate were obtained from JRS PHARMA GMBH & Co., KG and Nacalai Tesque Ltd., respectively. All other chemicals were of reagent grade and were used without further purification.

**Preparation of Solid Dispersion Granules** Table 1 shows PCS formulations used in this study. Granules were prepared using NIF, PCS, and binder in ratios specified in Table 1. NIF (7 g) was dissolved in an appropriate amount of ethanol (98–154 g) by heating at 60°C. The solution was added to PCS (35–56 g) and mixed for 5 min with a high-speed mixer granulator (High-Speed Mixer, EARTHTECHNICA Co., Ltd., Tokyo, Japan) at 250 rpm with an agitator and 2500 rpm with a chopper. Binder (49–122.5 g) dissolved in distilled water (21–62 g) by heating at 60°C added to this mixture to prepare the granules, and the granulation end point was determined visually. The granules were dried at 70°C for 12 h and pulverized in a speed mill (Okada Seiko Co., Ltd., Tokyo, Japan).

**Preparation and Evaluation of Tablets** Tablets were prepared using the mixture of granules, silicified microcrystalline cellulose, crospovidone and magnesium stearate in ratios specified in Table 1. The total weight of the mixture was 100 g. The granules (53.6–91.1 g) were mixed with silicified microcrystalline cellulose (3.4–40.9 g) and disintegrant (5 g) using a V-blender (S-5, Tsutsui Scientific Instruments Co., Ltd., Tokyo, Japan) for 5 min, then the mixtures were further mixed with magnesium stearate (0.5 g) for 2 min. These mixtures were compressed using a rotary tableting machine (PICCOLA, Riva S.A., Buenos Aires, Argentina) with 8 mm diameter bi-convex punches at a rotating speed of 20 rpm. All batches of tablets weighed 280 mg and the target compression load for each batch was 3 kN.

The hardness of ten tablets was measured by the diametrical compression method and the mean values were calculated. Disintegration times of six tablets from each batch were measured individually in water at 37 ± 2°C using a Riken Disintegration Tester (Miyamoto Riken Ind., Co., Ltd., Osaka, Japan) and the mean values were calculated. Dissolution tests were performed according to the JP16 paddle method using a Riken Dissolution Tester (Miyamoto Riken Ind., Co., Ltd.). One tablet containing 10 mg of NIF was placed in dissolution medium (900 mL of distilled water) at 37 ± 0.5°C, and the paddle was rotated at 50 rpm. The amount of dissolved NIF was analyzed by HPLC using a Shimadzu LC-10ADvp pump (Shimadzu Corp., Kyoto, Japan), a Shimadzu SPD-20 A Detector (Shimadzu Corp.), set at 350 nm, and an Inertsil ODS-3 column (GL Sciences Inc., Tokyo, Japan, 4.6 × 150 mm, 3 μm). Three tablets were tested from each batch and the mean values were calculated. The NIF content was estimated by weighing and finely grinding ten tablets, then ground tablet powder equivalent to 10 mg of NIF was accurately weighed, dissolved, suitably diluted in methanol, and analyzed by HPLC. In this study, the drug release percentage was calculated from the ratio of the measured amount of dissolved NIF to the NIF content in the tablets.

**Preparation of Adsorption Solid Dispersion (ASD) and Physical Mixture (PM)** NIF (0.5 g) was dissolved in ethanol (7 g) by heating at 60°C, then this solution was added to PCS

**Table 1. Compositions in PCS Formulations**

<table>
<thead>
<tr>
<th>(mg/Tablet)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formula</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIF</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>PCS</td>
<td>70.0</td>
<td>70.0</td>
<td>70.0</td>
<td>70.0</td>
<td>50.0</td>
<td>60.0</td>
<td>80.0</td>
</tr>
<tr>
<td>Binder</td>
<td>140.0</td>
<td>70.0</td>
<td>105.0</td>
<td>175.0</td>
<td>100.0</td>
<td>120.0</td>
<td>160.0</td>
</tr>
<tr>
<td>Silicified microcrystalline cellulose</td>
<td>44.6</td>
<td>114.6</td>
<td>79.6</td>
<td>9.6</td>
<td>104.6</td>
<td>74.6</td>
<td>14.6</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>14.0</td>
<td>14.0</td>
<td>14.0</td>
<td>14.0</td>
<td>14.0</td>
<td>14.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>
(3.5 g) and mixed for 30 min with a rotation mixer. The mixture was dried for 12 h at 70°C. PM was prepared by mixing NIF (0.5 g) and PCS (3.5 g) for 30 min with a rotation mixer.

**Measurement of the Properties of Granules** The values of angle of repose of granules were measured using a rotating cylinder type apparatus (Tsutsui Scientific Instruments Co., Ltd.). Scanning Electron Microscopy (SEM; VE-8800, Keyence Co., Osaka, Japan) was employed to examine the morphology of granules particles formed during wet granulation. The particle size distributions of granules were measured by laser diffraction and the scattering method with a LS 13 320 (Beckman Coulter Inc., Tokyo, Japan).

**Powder X-ray Diffraction (PXRD) Analysis** PXRD analysis was performed with Cu radiation, a voltage of 40 kV and a current of 30 mA (SmartLab, Rigaku Corporation, Tokyo, Japan). The scan rate was 40°/min over a 2θ range of 5–90° with a sampling interval of 0.02°.

**Fourier Transform Infrared (FT-IR) Spectroscopy** FT-IR spectra were obtained using a spectrophotometer (IRAffinity-1; Shimadzu Co.) using the potassium bromide (KBr) pellet method. KBr disks were prepared by mixing several mg of sample with potassium bromide and compacting. The scan range was 4000 to 400 cm⁻¹.

**In Vivo Absorption Study in Rats** Male Waster rats (weight: 200–250 g; age: 11 weeks; Japan SLC, Shizuoka, Japan) were fasted overnight prior to the experiments but allowed free access to water. All the procedures used in the current study were conducted in accordance with the guidelines approved by the Institutional Animal Care and Ethical Committee of Mukogawa Woman’s University. The jugular vein of each rat was cannulated the day before drug administration. NIF, PM and granules (corresponding to an NIF dose of 2 mg/kg) were suspended in distilled water for oral administration. For intravenous administration, NIF solution was prepared by dissolving NIF in polyethylene glycol 400–ethanol–water (1:1:8) at a final concentration of 0.15 mg/mL. The NIF suspensions were administered orally (corresponding to a dose of NIF of 0.75 mg/kg) to the rats. Blood samples to a dose of NIF of 2 mg/kg) and intravenously (corresponding to a dose of NIF of 0.75 mg/kg) to the rats. Blood samples (250 µL) were taken from the jugular vein cannula at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4 and 6 h after oral administration and 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3 and 4 h after intravenous administration. Heparinized 0.9% NaCl-injectable solution (100 units/mL; 50 µL) was used to flush the cannula after each blood sampling to prevent blood clotting. No anesthesia procedure was used during sampling. The plasma samples were separated by centrifugation (4°C, 12000 rpm, 10 min) using a refrigerated top centrifuge and kept frozen at −20°C until analysis.

**Analytical Methods** Frozen plasma samples were thawed at room temperature just before sample preparation. One hundred microliters of plasma was mixed with 1 mL of acetonitrile and the mixture was centrifuged for 10 min (4°C, 12000 rpm). One milliliter of the supernatant was removed and evaporated to dryness. The residue was reconstituted in 100 µL mobile phase, and 50 µL was analyzed by HPLC at 236 nm using the equipment described above. The mobile phase consisted of acetonitrile–10 mM KH2PO4 in a 45:55 (v/v) ratio and the flow rate was 1.0 mL/min. All analyses were carried out at 40°C.

**Pharmacokinetic Analysis** Maximum blood concentration (Cmax) and the time required to reach the maximum blood concentration (Tmax) were determined directly from the plasma concentration–time data. The area under the plasma concentration–time curve (AUC) from time zero to infinity was calculated using a pharmacokinetic analysis computer program.²²

**Statistical Analysis** All results are presented as the mean±standard deviation (S.D.). All statistical analyses were performed using Statcel for Windows (The publisher OMS Ltd., Saitama, Japan). One-way ANOVA followed by Tukey–Kramer test was used for multiple comparisons. Differences were considered significant when the calculated p value was less than 0.05.

**Results and Discussion**

**Selection of Binder and Disintegrant for the Tableting Process** As stated earlier, the low density of PCS (0.07 g/cm³) allows it to easily become airborne, making its use in tablet manufacture difficult and requiring the preparation of higher density PCS. Hirai et al. suggested that wet granulation combined with the use of a saccharide effectively improves the properties of low density PCS.²¹ To prepare the high density granules containing PCS and NIF with a wet granulation method by a high-speed mixer granulator, seven saccharides (dextrin, trehalose, lactose, sorbitol, glucose, fructose, and xylitol) were selected. The granules were prepared based on formula 1 (Table 1). These saccharides were dissolved in distilled water to mix uniformly with PCS, and to eliminate the difference in the powder properties of saccharides. The shape and density of the granules were similar among these saccharides (data not shown). Figure 1 shows the dissolution profiles of NIF from the different granules. The dissolution rates from granules prepared with sorbitol, fructose and xylitol were higher than the others, and the dissolution rate with dextrin was the lowest. The surface of granules prepared with fructose and glucose became brown after the drying process. Eichner et al. reported that a browning reaction of sugar (glucose and fructose) is accelerated by the addition of water,²³ suggesting that water in the granules enhanced the browning reaction during drying. It was difficult to make a hard tablet from granules prepared with sorbitol due to sticking during high pressure tableting. Based on these considerations, xylitol was selected as the binder for the granulation of PCS.

**Fig. 1. Effects of Binder on the Dissolution Profiles of NIF from Granules**

Dextrin (●); trehalose (▲); lactose (■); sorbitol (●); glucose (○); fructose (▲); xylitol (□). Each symbol represents the mean±S.D. (n=3).
Figure 2 shows SEM photographs of PCS, ASD, and granules prepared using formula 1 with xylitol. The mean particle sizes of PCS, ASD, and granules were 30.83, 31.18, and 431.2 (µm), respectively. The SEM photographs of PCS showed a rough surface due to the porous structure. The shape and particle size of ASD was similar to PCS, whereas granules had a large particle size due to form agglomeration of xylitol and ASD. In addition, PCS had a low bulk density (0.07 g/cm³) and a good angle of repose (39.5°). Granules had a high bulk density (0.38 g/cm³) and a good angle of repose (39.4°), suggesting that these granules have good density and flow properties for tableting.

Four disintegrants (crospovidone, low substituted hydroxypropyl cellulose (L-HPC), croscarmellose sodium and sodium starch glycolate) were investigated by preparing tablets with xylitol granules and each disintegrant (formula 1, Table 1). Crospovidone was the best disintegrant under the conditions tested (Fig. 3), and was thus selected as the disintegrant.

Effects of Amount of Binder and PCS on Tablet Properties The formulation was optimized by investigating the effect of amount of excipient on the dissolution of NIF from tablets. Four formulations were compared (formulas 1 to 4, Table 1) and the ratio of binder to PCS was varied from 1:1 to 2.5:1 to determine a suitable ratio of binder to PCS. Similar dissolution rates were observed between formulas 1, 3 and 4 (Fig. 4) whereas the dissolution rate from formula 2 was slower. The disintegration times of these formulations were within 10 min, and the thickness of all tablets was 6 mm,

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**Figure 2.** SEM Photographs of (A) PCS, (B) ASD, and (C and D) Granules
Granules prepared using xylitol as binder.

**Figure 3.** Effects of Disintegrant on the Disintegration Time of Tablets
Each column represents the mean±S.D. (n=6). *p<0.05 by Tukey–Kramer test.

**Figure 4.** Effect of Amount of Binder on the Dissolution Profiles of NIF from Tablets
Formula 2 (●); formula 3 (▲); formula 1 (■); formula 4 (♦). Each symbol represents the mean±S.D. (n=3).
and the tablet hardness of formulas 1, 2, 3, and 4 were 119, 119, 81, and 138 (N), respectively. These tablets properties may not affect the dissolution rates of NIF from tablets. The amount of binder in formula 2 is the lowest, and the amount of silicified microcrystalline cellulose is the highest. Silicified microcrystalline cellulose was added in formulation during tableting as weight correction. The differences of the tablet properties between these formulations were not observed, suggesting that the amount of silicified microcrystalline cellulose has little effect on dissolution rate of NIF from tablets. While, a weak binding force associated with lowest amount of binder may lead to a long granulation time. The granulation times of formulas 1 to 4 were 26, 91, 55 and 22 min, respectively. Ohno et al. reported that an increase in granulation time using

<table>
<thead>
<tr>
<th>Formula</th>
<th>Amount of ethanol (g)</th>
<th>Amount of added water (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-I</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1-II</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>1-III</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>1-IV</td>
<td>2</td>
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</tr>
<tr>
<td>1-V</td>
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<td>2.9</td>
</tr>
<tr>
<td>1-VI</td>
<td>2.6</td>
<td>2.9</td>
</tr>
<tr>
<td>1-VII</td>
<td>3.2</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Compositions of tablets is based on Table 1, formula 1.

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**Fig. 5. Effect of Amount of PCS on the Dissolution Profiles of NIF from Tablets**

Formula 5 (●); formula 6 (▲); formula 1 (◼); formula 7 (♦). Each symbol represents the mean ± S.D. (n=3).

**Fig. 6. Effect of Amount of Added Water on the Dissolution Profiles of NIF from Tablets**

Formula 1-I (●); formula 1-II (▲); formula 1-III (◼); formula 1-IV (♦). Each symbol represents the mean ± S.D. (n=3).

**Fig. 7. Proposed Figures for Surface Imaging of PCS Are Schematically Depicted**

Ethanol has a low surface tension and penetrates deeply into the pores of PCS, but water has a high surface tension and cannot penetrate deeply. At a low amount of ethanol ((A), (B)), NIF dissolved in ethanol penetrates deeply into the pores of PCS. Thus, added water has little effect on NIF dissolved in ethanol. At a large amount of ethanol (C), NIF dissolved in ethanol fills the pores of PCS. NIF contacts with added water because NIF is present in the whole pores of PCS. In the cases (B) and (C), the granules were prepared by adding the binder solution to NIF adsorbed on PCS after removing the ethanol by drying to equalize granulation condition.
a high-speed mixer granulator led to a decreased dissolution rate; this may explain the slow dissolution rate from formula 2. Namely, the dissolution rate might have been decreased by the slow disintegration of granules rather than that of tablets, due to the consolidation of the granules as the granulation times increased. Ohno et al. also suggested that dissolution rate decreased with an increase in binder liquid, in contrast to the current results. We used both ethanol and water during wet granulation, whereas Ohno et al. used water only. Millili and Schwartz reported that granules produced using water alone had a higher mechanical strength than granules produced using a mixture of ethanol and water (70:30), suggesting that the binding force of xylitol may have been decreased by the influence of ethanol in the current study. Thus, the amount of binder may be little effect on dissolution rate of tablet using PCS.

The effects of the amount of PCS on the dissolution profile of tablets (formulas 1, 5–7, Table 1) are shown in Fig. 5. The disintegration times of these formulations were within 10 min, and the thickness of all tablets was 6 mm, and the tablet hardness of formulas 1, 5, 6, and 7 were 119, 99, 144, and 76 (N), respectively, showing that tablets properties were little difference between these formulations. The dissolution rate improved as the amount of PCS increased, due to facilitated interaction of NIF with PCS as the amount of PCS increased. Also, the large surface area of PCS for drug adsorption reduces the chances of drug particle agglomeration. Since PCS easily disperses in aqueous media, the wettability of the drug might be improved in aqueous conditions.

Effects of Amount of Added Water and Ethanol on Tablet Properties The interaction of NIF and PCS is likely important to the dissolution rate of NIF since the solid dispersion of a poorly water-soluble drug in PCS improves the dissolution rate of the drug. PCS can absorb a very large amount of liquid (4–6 mL/g). Added water acts as a binder but its effects on the deformability of the granules should be taken into account. Thus, the amount of added water and ethanol likely affects the dissolution rates of NIF from the tablets.

Figures 6 and 7 show the dissolution profiles of NIF from these formulations. The dissolution rates of NIF from PCS formulations (tablet and granules) improved and were comparable to those of the original NIF. As mentioned above, ethanol may reduce the binding force of xylitol and decrease the effect of added water on the dissolution rate. The structure of PCS comprises assembled petal-like flakes and can absorb a large amount of liquid. Ethanol has a low surface tension and might penetrate deeply into the petal-like flakes of PCS, whereas the high surface tension of water may prevent its deep penetration. The above results support case (A) in Fig. 7 because the volume of ethanol used in formulas 1-I to -IV is the minimum amount required to dissolve NIF. Tablets (formulas 1-V to -VII, Table 2) were prepared to estimate the effect of ethanol on the rate of dissolution. The volume of ethanol in formula 1-VII is the maximum amount that PCS can absorb. To equalize granulation condition such as amount of added water, the granules were prepared by adding the binder solution to NIF adsorbed on PCS after removing the ethanol by drying (cases (B), (C) in Fig. 7). No significant differences in the dissolution rate of the tablets were observed. The effect of added water on the dissolution rate of NIF from formula 1 is not observed, suggesting that NIF adsorbed on the PCS may be not recrystallized. Thus, the dissolution rates of several NIF formulations were compared to estimate further the effect of water.

Figure 8 shows the dissolution profiles of NIF from these formulations. The dissolution rates of NIF from PCS formulations (tablet and granules) improved and were comparable to those of the original NIF.
to that of ASD. The dissolution % of pure drug and PM at 120 min were lower than 20%, but the values of ASD, granules, and tablet were about 70% at 30 min, showing that the dissolution rates of NIF increased in the solid dispersion compared to pure drug and PM. Recrystallization due to moisture is a major drawback of most solid dispersion formulations, so the wet granulation method is generally not suitable for the preparation of solid dispersion formulations. Remarkably, the dissolution rates of tablets and granules prepared using water were similar to that of ASD prepared without using water. These results indicate that solid dispersions prepared by the wet granulation method exhibit improved drug dissolution to the same degree as preparations made using the dry granulation method and that PCS may inhibit recrystallization of the solid dispersion due to water.

**Evaluation of NIF in PCS Formulations**

PXRD patterns were obtained to determine the crystallinity of NIF in the PCS formulations (Fig. 10). PM showed low intensity PXRD peaks arising from NIF. Whereas, PXRD peaks arising from NIF were not present in ASD, suggesting that NIF is present in the amorphous state in PCS. Also in PCS formulations (granules), PXRD peaks arising from NIF were disappeared, suggesting that NIF is not recrystallized in formulations.

FT-IR spectra were obtained to determine the interactions between NIF and PCS (Fig. 11). The FT-IR spectrum of pure NIF (Fig. 11(A)) showed characteristic peaks at 1678/1690 cm\(^{-1}\) (C=O stretching) and 3327 cm\(^{-1}\) (secondary –NH). Some of these characteristic peaks are observed in PM (Fig. 11(B)) but are essentially absent in the PCS formulation (tablet) and ASD (Figs. 11(C), (D)), revealing that C=O and NH are involved in the interaction between NIF and PCS. The FT-IR spectrum of PCS (Fig. 11(E)) did not show a sharp peak in the range of them. Hydrogen bonding between N–H groups of NIF and a water-soluble carrier, such as PVP and HPMC, have been reported. In addition, Sharma *et al.* and Kinoshita *et al.* reported hydrogen bonding between the silanol group of PCS and C=O groups of the drug, suggesting that decreased crystallinity of NIF might be associated with hydrogen bonding between the C=O/NH groups of NIF and the silanol group of PCS.

The above results suggest that NIF is in the amorphous state following the preparation of granules with PCS by a wet granulation method using water.
The plasma concentration of NIF after dosing with granules was 3.9, 10.6, and 137.6 µg/L, respectively. The bioavailability of granules was 13.7-fold greater than those of NIF powder, PM and granules after preparation by a wet granulation method using water. The wet granulation method proposed here is very effective in improving the dissolution rate and bioavailability of poorly water-soluble drugs.

Table 3. Comparison of the Mean Pharmacokinetic Parameters of NIF after a Single Oral Administration of NIF, PM and Granules (Formula 1) in Rats

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/L)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC (µg·h/L)</th>
<th>BA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIF (2 mg/kg)</td>
<td>92.2±24.1</td>
<td>0.67±0.14</td>
<td>498.6±160.7</td>
<td>12.1±3.9</td>
</tr>
<tr>
<td>PM (NIF 2 mg/kg)</td>
<td>142.1±49.9</td>
<td>0.81±0.24</td>
<td>436.3±137.6</td>
<td>10.6±3.3</td>
</tr>
<tr>
<td>Granules (Formula 1) (NIF 2 mg/kg)</td>
<td>953.3±120.0*</td>
<td>0.94±0.13</td>
<td>1832.3±317.8*</td>
<td>44.5±7.7*</td>
</tr>
</tbody>
</table>

Data are the mean±S.D. (n=3–4). *p<0.05 vs. NIF and PM by Tukey–Kramer test.

**Evaluation of in Vivo** Figure 12 shows the plasma concentrations of NIF after a single oral administration of either NIF powder, PM, or granules (formula 1, Table 1) at a dose equivalent to 2 mg/kg of the drug, and Table 3 lists the pharmacokinetic parameters calculated from the NIF profiles following oral and intravenous administration (data not shown). The plasma concentration of NIF after dosing with granules was markedly greater than those after dosing with NIF powder or PM. The C<sub>max</sub> of NIF powder, PM and granules were 92.2±24.1, 142.1±49.9 and 953.3±120.0 (µg/L), respectively. The AUC of NIF powder, PM and granule were 498.6±160.7, 436.3±137.6 and 1832.3±317.8 (µg·h/L), respectively. The C<sub>max</sub> and AUC values of granule were 10.3- and 3.7-fold greater than those of NIF powder. The oral bioavailability of NIF from NIF powder, PM and granules were 12.1±3.9, 10.6±3.3 and 44.5±7.7 (%), respectively. The bioavailability of granules was 3.7-fold greater than those of NIF powder. Funakoshi et al. reported an oral bioavailability of NIF solution of 46.0±7.7 (%), very similar to the value for granules. The *in vivo* and *in vitro* results presented here clearly indicate the usefulness of formulating NIF with PCS using wet granulation.

**Conclusion** Solid dispersion formulations of NIF with PCS using the wet granulation method were prepared and evaluated. These formulations exhibited much higher dissolution rates than NIF powder, comparable to ASD. Furthermore, these formulations provided superior bioavailability in rats compared with NIF powder. NIF was present in the amorphous state in the granules after preparation by a wet granulation method using water. The wet granulation method proposed here is very simple and may be applicable to other poorly water-soluble drugs.

**Conflict of Interest** The authors declare no conflict of interest.

**References**