Clopidogrel Napadisilate Monohydrate Loaded Surface-Modified Solid Dispersion: Physicochemical Characterization and in Vivo Evaluation

Young Hun Kim, Dong Wuk Kim, Min Seok Kwon, Kwan Hyung Cho, Jong Oh Kim, Chul Soon Yong and Han-Gon Choi

College of Pharmacy & Institute of Pharmaceutical Science and Technology, Hanyang University; College of Pharmacy, Yeungnam University; College of Pharmacy, Inje University

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To develop a novel solid dispersion of clopidogrel napadisilate monohydrate (CNM) with improved stability and oral bioavailability, surface-modified solid dispersions were prepared by spray-drying using water as a solvent, Tween 80 as a surfactant, and hydroxypropylmethyl cellulose (HPMC) as a hydrophilic polymer, and optimized according to drug solubility. Its solid-state characterization was evaluated by scanning electron microscopy (SEM), powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC). The stability study was performed at 50°C/75% RH over a period of 6 weeks. Its dissolution profiles and oral bioavailability in rats were also compared with that of CNM and clopidogrel bisulfate (CB). The solid dispersion, composed of CNM/HPMC/Tween80 at a weight ratio of 10/2.5/2.5, in which CNM was in the crystalline state, increased the drug solubility approximately 4.6-fold. It showed a significantly better dissolution profile than that of CNM in all the dissolution media, and gave either similar or higher dissolution compared to that of CB. This solubility and dissolution enhancement was attributed to improved wetting and solubilization of CNM crystals due to hydrophilic carriers attached on the drug surface. It had excellent stability, thereby addressing the stability problem of CB powder. Furthermore, it increased the area under curve (AUC) values by about 4-fold and 1.6-fold compared to CNM and CB, respectively, suggesting that it improved the oral bioavailability of the drug in rats. Thus, this solid dispersion system prepared with water, HPMC and Tween 80 can be used to enhance the bioavailability of CNM as well as to solve the stability problem of CB.

Key words: clopidogrel napadisilate monohydrate; surface-modified solid dispersion; water; stability; bioavailability

Clopidogrel, a non-competitive inhibitor of adenosine diphosphate in platelets is an orally administered antiplatelet agent prescribed for cerebral and peripheral vascular diseases and for the early and long term secondary prevention of atherothrombotic events in patients with acute coronary syndromes. This drug is practically insoluble in water; hence, its commercial salt form, clopidogrel bisulfate (CB) has been widely used in the pharmaceutical industry. CB is highly soluble in water and rapidly absorbed in vivo; however, this salt form is slightly hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; 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however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly absorbed; however, this salt form is slight hygroscopic and has been reported not soluble in water and rapidly applied to the drug surface, converting the hydrophobic drug surface into hydrophilic surfaces. In surface-modified solid dispersion, the solubility of the drug is increased by the attachment of hydrophilic carriers (hydrophilic polymer and surfactant) onto the drug surface, thus facilitating the solubility and dissolution of the drug. This technique is a favored technique to increase the aqueous solubility of poorly water-soluble drugs by dispersing the drug in a hydrophilic carrier via solvent evaporation, solvent wetting or melting methods. However, in these methods, there are some limitations with the choice of drug and formulation dose, and the high temperature of the melting method may affect the stability of the active ingredient of the formulation. Moreover, the solvent evaporation and wetting methods may lead to unstable formulations as they will change the crystalline drug into an amorphous form. Apart from these disadvantages, in the conventional solid dispersion technique, a high polymer ratio is used. However, a novel surface-modified (surface-attached) solid dispersion method has been reported to overcome the disadvantages of conventional solid dispersion techniques. In this solid dispersion technique, a low carrier to drug ratio is used and, importantly, water is used as the solvent instead of an organic solvent. In surface-modified solid dispersion, the solubility of the drug is increased by the attachment of carriers (hydrophilic polymer and surfactant) onto the drug surface, converting the hydrophobic drug surface into hydrophilic, thus facilitating the solubility and dissolution of the drug. Since there is no crystalline change and water is used as the solvent while spray drying the solid dispersion, the industrial feasibility is high for this solid dispersion technique.

In this study, we investigated the surface-modified solid dispersion technique for a poorly water-soluble salt, CNM, to formulate a stable formulation with increased oral bioavailability. In our previous study, we developed a CNM-loaded surface-modified solid dispersion with Cremophor and hydroxypropylmethyl cellulose (HPMC) as a surfactant and

* These authors contributed equally to this work.

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hydrophilic polymer, respectively.\textsuperscript{9} Cremophor, a polyoxyethylene castor oil derivative, has been widely used excipients in oral and intravenous pharmaceutical products to improve drug dissolution and absorption.\textsuperscript{10} However, it was reported to induce severe toxic side effects, on endothelial and epithelial cells, resulting that several serious anaphylactic reactions, cardiotoxicity, and neurotoxicity was observed in humans and animals.\textsuperscript{11,12} Thus, another CNM-loaded surface-modified solid dispersion was prepared using Tween 80 as a surfactant instead of Cremophor. The solid dispersion formulations were investigated regarding solubility, dissolution, scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). Moreover, its stability was compared to that of CNM and CB powder. The oral bioavailability of the optimized solid dispersion in rats was also compared with that of CNM and CB.

MATERIALS AND METHODS

Materials Two salts, CNM and CB, were kindly supplied by Hanmi Pharm. Co. (Hwasung, South Korea). Hydroxypropylmethylcellulose (HPMC, 2910) and polysorbate 80 (Tween 80) were purchased from Shin-Etsu Co. (Tokyo, Japan) and Duksan Chemical Co. (Ansan, South Korea), respectively. All other chemicals were of reagent grade and were used without further purification.

Preparation of Surface-Modified Solid Dispersions A Büchi Mini Spray Dryer (B-290; Flawil, Switzerland) was employed for the preparation of CNM-loaded solid dispersions. Various ratios of Tween 80 and HPMC were dissolved in 1L of water. Then, the drug pre-sieved through 50 mesh sieves was dispersed into each solution (Table 1). Each resulting suspension with non-dissolved drug was continuously stirred and transferred to a 0.7 mm pneumatic nozzle using a peristaltic pump and spray-dried, leading to producing the CNM-loaded solid dispersions. The spray-drying conditions were as follows: inlet and outlet temperature, 150 and 75–85°C; feeding rate, 5 mL/min; aspiration, 100%.

Solubility of Clopidogrel in Solid Dispersions An excess amount of CNM-loaded solid dispersions (equivalent of about 100 mg of CNM powder) was added to distilled water, agitated at 25°C for 7 d and centrifuged at 13000 × g for 5 min (5415C; Eppendorf, Hamburg, NY, U.S.A.). The supernatant layer was diluted and passed through a 0.45 µm membrane filter. The concentration of CNM in the filtrate was assayed by an Agilent 1260 Infinity LC system (Agilent Technologies; Santa Clara, CA, U.S.A.) equipped with Agilent ChemStation computer software, an Agilent 1260 Quat pump, an Agilent 1260 VWD detector and an Inertsil ODS-4 reverse-phase C18 column (GL Science, 250 mm × 4.6 mm i.d., 5 µm). The mobile phase consisted of methanol and distilled water (90:10, v/v). The mobile phase was maintained at 220 nm with a flow rate of 1 mL/min. In this HPLC method, the inter- and intra-day variance were within the acceptable range (R²=0.999).\textsuperscript{31}

Morphological Characterization of Surface-Modified Solid Dispersion The surface morphology of the drug and solid dispersion was examined by SEM (S-4800; Hitachi; Tokyo, Japan). Samples were affixed onto a brass specimen holder using double-sided adhesive tape, and the powders were made electrically conductive by coating with platinum (6nm/min) in a vacuum (0.8 Pa) using an EmiTeck Sputter Coater (K575 K) for 4 min at 15 mA.

Structural and Thermal Investigation of Surface-Modified Solid Dispersion The XRD measurements of the samples were collected on a D/MAX-2500 powder X-ray diffractometer instrument (Rigaku, Japan) equipped with a copper anode operated with CuKa radiation (1.54178 Å, 40 kV and 100 mA). Patterns were collected using a step width of 0.02/° over a range from 3.5° to 40° at room temperature on a 2θ scale. In addition, DSC measurements were conducted using a TA DSC Q20 instrument (TA Instruments; Newcastle, DE, U.S.A.). Samples were weighed in Tzero pans & lids (5 mg) and heated from 150°C to 240°C at a heating rate of 10°C/min under a nitrogen gas purge (50 mL/min).

Stability of CB, CNM and CNM-Loaded Solid Dispersion The CNM-loaded solid dispersion, CB and CNM powder samples were placed in a closed glass containers and exposed to 50°C/75% RH for 6 weeks. The drug content, hydrolyzed degradants and racemized degradants in the solid dispersion were assayed by an Agilent 1260 Infinity LC system (Agilent Technologies; Santa Clara, CA, U.S.A.) equipped with Agilent ChemStation (Rev. B. 04.03) computer software, an Agilent 1260 Quat pump, an Agilent 1260 VWD detector and an Ultron ES-OVM column (Rockland Technologies, 150 mm × 4.6 mm i.d., 5 µm). The mobile phase consisted of pH 4.8 phosphate buffer and acetonitrile (80:20, v/v). These mobile phases were eluted at 220 nm with a flow rate of 1 mL/ min. In this HPLC method, the inter- and intra-day variance were within the acceptable range (R²=0.999). In addition, the water content was assayed by thermogravimetric analysis (TGA Q50; TA Instruments).

Dissolution of CB, CNM and CNM-Loaded Solid Dispersion Dissolution studies were performed with 900 mL of distilled water, 0.1 N HCl (pH 1.2) and phosphate buffered solutions (pH 4.0 and 6.8) as dissolution media at 36.5°C. CNM-loaded solid dispersions, CNM and CB (equivalent to 20 mg of clopidogrel) were loaded in 5 size gelatin capsules and placed in the dissolution vessels (Vision G2 Classic 6; Hansob Technology, Chatsworth, CA, U.S.A.) equipped with baskets rotating at 100 rpm. At predetermined intervals, 1 mL of the medium was sampled and filtered through a membrane filter (0.45 µm). The concentrations of clopidogrel in the samples were quantified by HPLC as described in solubility study section.

Pharmacokinetic Studies Eighteen male Sprague-Dawley rats (7–9 weeks old, weighing 260–300 g) were purchased from the Nara Biotech (Seoul, South Korea). Prior to the

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug (g)</th>
<th>HPMC (g)</th>
<th>Tween 80 (g)</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>9</td>
<td>1</td>
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<tr>
<td>III</td>
<td>10</td>
<td>8</td>
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<td>IV</td>
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<td>7</td>
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<td>V</td>
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<td>VII</td>
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<td>2.5</td>
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<tr>
<td>IX</td>
<td>10</td>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td>X</td>
<td>10</td>
<td>0.5</td>
<td>0.5</td>
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</tbody>
</table>
experiments, these animals were maintained at room temperature with a relative humidity of 50±5%. All animal care and procedures were performed in accordance with the guidelines and protocols approved by the Institute of Laboratory Animal Resource, Hanyang University. Eighteen rats were divided into three groups. Each rat was anesthetized with mixture of zoletil and rompun (2:1) and secured on a surgical board in the supine position with a thread. The solid dispersion, CB and CNM were individually administered by oral gavage at a dose of equivalent to 30mg/kg of clopidogrel base under 12h fasting conditions. Approximately, 0.35mL of blood was sampled via the femoral artery at predetermined time intervals. Then, it was centrifuged at 3000×g for 10min to separate the plasma. The plasma samples were stored at –20°C until further studies. To 160µL of plasma, 20µL of the internal standard (atorvastatin in methanol, 120µg/mL) and 1500µL of methanol were added to extract SR26334 (major metabolite of clopidogrel). The methanol extract was vacuum centrifuged and the residue was reconstituted with 80µL of solvent (ethanol–water, 60:40). Then, 50µL of the sample was analyzed by HPLC (Agilent Technologies) equipped with an Inertsil ODS-4 reverse-phase C18 column (GL Science, 250mm×4.6mm i.d., 5µm) and an Agilent 1260 VWD detector. The mobile phase was composed of methanol–0.05% TFA (75:25, v/v). The eluent (1.0mL/min) was monitored at 220 nm for SR26334 detection. 2,3) All pharmacokinetic parameters including area under the plasma concentration–time curve (AUC), maximum plasma concentration (Cmax), time to reach the maximum plasma concentration (Tmax), half-life (t1/2) and elimination rate constant (Kel) were estimated by the WinNonlin™ (Pharsight Corp., Mountain View, CA, U.S.A.) program. Levels of statistical significance (p<0.05) were evaluated using the ANOVA test between the formulations. All values were expressed as the mean±standard deviation (S.D.).

RESULTS AND DISCUSSION
Preparation of Clopidogrel Napadisilate Monohydrate-Loaded Solid Dispersion The surface-modified solid dispersion was prepared with a hydrophilic polymer and a surfactant by the spray drying technique. In this preparation, HPMC and Tween 80 were used as the hydrophilic polymer and the surfactant, respectively. In the preliminary study, the solubility studies were performed by introducing an excess amount of CNM to various surfactants or aqueous solutions of the 1% hydrophilic polymer. HPMC (4567.6±666.5µg/mL) and Tween 80 (5628.4±55.8µg/mL) increased drug solubility

Fig. 1. Solubility of CNM in Various Solid Dispersions
Each value represents the mean±S.D. (n=3). *p<0.05 by Student’s t-test.

Fig. 2. Scanning Electron Micrographs
(A), drug powder (2000×); (B), HPMC (500×); (C), solid dispersion (3000×).
Fig. 3. X-Ray Powder Diffraction
(A), drug powder; (B), HPMC; (C), physical mixture; (D), solid dispersion.

Fig. 4. Differential Scanning Calorimetric Thermograms
(A), drug powder; (B), HPMC; (C), physical mixture; (D), solid dispersion.

Fig. 5. Stability Profile of CNM, CB and the Solid Dispersion under Accelerated Conditions
(A), water content; (B), drug content; (C), hydrolyzed degradant; (D), racemized degradant. Each value represents the mean±S.D. (n=3). *p<0.05 compared to CNM and solid dispersion.
to the greatest degree among the tested hydrophilic polymers and surfactants (data not shown). In addition, these carriers have been widely used as additives in the pharmaceutical industry, and are regarded as non-toxic and non-irritant ingredients.

In order to optimize the ratio between the polymer and surfactant, the surface-modified solid dispersions were prepared using various polymer to surfactant ratios with a constant amount of the drug (Table 1). First, the effect of the ratio between HPMC and Tween 80 on the solubility of CNM in the solid dispersion was examined (Table 1, Fig. 1, formulations I to VII). It was observed that an increase in Tween 80 increased the solubility of the drug in the solid dispersion to 6:4, followed by no significant differences in drug solubility. Additionally, formulations I–VI were not sticky and adhesive. However, formula VII gave adhesive particles due to relatively larger amounts of Tween 80, a liquid surfactant. At the 5:5 (HPMC/Tween 80) ratio, the solid dispersion with non-adhesive particle showed the most significant increase in CNM solubility among formulations I–VII; hence, the polymer/surfactant ratio was fixed at 5:5. Noticeably, Formulaion I prepared with only HPMC showed significantly lower drug solubility compared to the drug solubility in 1% HPMC aqueous solution tested in preliminary study (1977.3±78.4 µg/mL). In performing of the solubility studies, the amounts of HPMC were equal to those of drug in Formulation I, while very large amounts of HPMC were used against those of drug in the latter. Thus, HPMC, a hydrophilic polymer had a limited improvement in drug solubility.

To determine the ratio between CNM to the surfactant/polymer mixture, solid dispersions VI, VIII to X were prepared by varying the carrier amount in the solid dispersion (Table 1). The aqueous solubility of drug was increased with increased amount of carriers to 0.5 (Fig. 1; X vs. IX vs. VIII). However, the formula VI with the amount of carriers of 1.0 hardly improved the drug solubility compared to formula VIII with the amount of carriers of 0.5, even though they were not significantly different. These observations revealed that an optimized amount of polymer and surfactant is needed to improve the solubility of CNM in the solid dispersion. Therefore, solid dispersion VIII was selected for further studies as it increased the solubility of CNM significantly by about 4.6-fold compared to that of CNM powder (6775.1±2686.9 µg/mL) with a low carrier content.

Characterization of Surface-Modified Solid Dispersion

The scanning electron micrographs of CNM powder and the solid dispersion are given in Fig. 2. CNM powder (Fig. 2A) had a crystalline appearance with smooth surface. HPMC...
(Fig. 2B) gave an irregular shape with rough surface. In the preparation of this surface-modified solid dispersion, HPMC and Tween 80 were entirely dissolved in water while drug was suspended. On spray drying, both carriers were attached on the surface of undissolved drug. CNM loaded solid dispersion appeared relatively coarse with a fissured surface, suggesting that the carriers were adhered onto the surface of the drug particles.

The PXRD patterns of CNM had sharp peaks, indicating a typical crystalline pattern of the drug (Fig. 3A). HPMC showed no intrinsic peaks (Fig. 3B). In the physical mixture (Fig. 3C) and solid dispersion (Fig. 3D), the features of all major representative peaks detected in the drug appeared, indicating that the drug was present in unchanged crystalline form in the solid dispersion.

Thermal behaviors are shown in Fig. 4. CNM showed an endothermic peak at about 230°C, indicating the typical crystallinity of CNM (Fig. 4A). HPMC gave no peaks (Fig. 4B). An endothermic peak of CNM appeared in the physical mixture (Fig. 4C), while the endothermic peak of the drug (Fig. 4D) was shifted a little in the solid dispersion, suggesting that there was an interplay of the drug and polymer in the solid dispersion at high temperatures. These findings revealed that the drug in this surface-modified solid dispersion was in crystalline form.

Stability of CB, CNM and CNM-Loaded Solid Dispersion

The stability of the drug in the solid dispersion, CB and CNM was estimated at the water content, drug content, hydrolyzed degradants and racemized degradants after 6 weeks of storage at 50°C/75%RH (Fig. 5). At week 0, CB showed a negligible water content (0%) owing to its anhydrous property (Fig. 5A). It gave no significant changes in water content up to 2 weeks followed by a slight increase in the water content, suggesting its hygroscopic nature. CNM showed a water content of approximately 2% at week 0 due to its monohydrated property, but showed no significant changes in the water content until 6 weeks, indicating its non-hygroscopic property. On the other hand, the solid dispersion had a higher water content of about 3% powder at the initial time point, because distilled water was used in its preparation. In addition, this solid dispersion showed an increased water content over time, since the carriers, HPMC and Tween 80, were hydrophilic. The drug content study revealed that CB salt is highly unstable under accelerated conditions, since at the end of 6 weeks, the drug content in CB had decreased by about 50% (Fig. 5B). CNM and the solid dispersion showed no changes in the drug content over the test period, suggesting that CNM and the solid dispersion were stable under the experimental conditions.

The hydrolyzed (Fig. 5C) and racemized (Fig. 5D) degradants were significantly increased in CB at the end of 6 weeks. Particularly, the hydrolyzed and racemized degradants in CB increased to approximately 50% and 6% at 6 weeks, respectively, indicating that CB was unstable in this condition. However, CNM and the solid dispersion had significantly lower degradant amounts compared to that of CB. Based on these stability studies, the stability of the clopidogrel salt form depends upon its hygroscopic nature. Even if the external environment contained a relatively high water content, CNM was very stable under accelerated conditions due to its non-hygroscopic nature. However, the hygroscopic property of CB salt led to drug instability under accelerated conditions.

Dissolution of CB, CNM and CNM-Loaded Solid Dispersion

To assess the performance of the solid dispersion compared to that of CNM and CB powders, dissolution studies were performed in water and in dissolution media at pH 1.2, pH 4.0 and pH 6.8 (Fig. 6). At pH 1.2, CB showed a maximum dissolution rate within 10 min; however, by 60 min, all the formulations were maximally dissolved (Fig. 6A). At pH 4, CB and the solid dispersion showed a higher than 90% dissolution rate by 30 min; however, CNM had a poor dissolution profile, since less than 20% of the drug dissolved from the CNM powder (Fig. 6B). At pH 6.8, the solid dispersion had a higher dissolution rate at 60 min than that of CB (about 55% vs. 42%) (Fig. 6C). In water, the solid dispersion and CB showed almost 100% dissolution by 60 min, but CNM showed only about 50% dissolution by 60 min (Fig. 6D). Moreover, the equilibrium solubility of CNM powder in water at 25°C is about 1450 µg/mL; however, the dissolution amounts of

Table 2. Pharmacokinetic Parameters

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<thead>
<tr>
<th>Formulations</th>
<th>AUC (h·ng/mL)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>K&lt;sub&gt;el&lt;/sub&gt; (h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNM</td>
<td>527.3±147.4</td>
<td>100.0±38.5</td>
<td>1.0±0.4</td>
<td>4.4±1.3</td>
<td>0.2±0.1</td>
</tr>
<tr>
<td>CB</td>
<td>1295.1±310.9*</td>
<td>310.2±67.1*</td>
<td>1.0±0.4</td>
<td>2.5±0.7</td>
<td>0.2±0.1</td>
</tr>
<tr>
<td>Solid dispersion</td>
<td>2122.7±478.4*</td>
<td>320.0±84.6*</td>
<td>1.3±0.2</td>
<td>3.7±1.0</td>
<td>0.2±0.1</td>
</tr>
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</table>

The solid dispersion was composed of CNM/HPMC/Tween 80 at a weight ratio of 10:2.5:2.5. *p<0.05 compared with CNM powder. **p<0.05 compared with CNM and CB powder. Each value represents the mean±S.D. (n=6).
CNM was 11 µg/mL in water at 37°C for 60 min (Fig. 6D). Like other poorly water soluble drugs, CNM took a long time to reach the equilibrium solubility.\textsuperscript{6–9} Our results indicated that CNM showed a decreased dissolution profile as the pH of the dissolution media increased. Moreover, the solid dispersion initially showed low dissolution in all dissolution media compared to that of CB; however, had a similar or superior dissolution profile at 60 min compared to CB.

**Pharmacokinetic Studies** The pharmacokinetics of the CNM-loaded solid dispersion was performed to assess whether the increased dissolution profile shown in the dissolution studies was reflected in vivo compared to CNM and CB powder. The mean plasma concentration profiles of the major metabolite of clopidogrel (SR26334) after oral administration of CNM, CB, and the solid dispersion at a dose of equivalent to 30 mg/kg of clopidogrel base in rats are shown in Fig. 7. Clopidogrel is a prodrug, thus it requires enzymatic conversion to exert its pharmacological effect. As clopidogrel is highly metabolized by cytochrome P450 enzymes and hydrolysis after oral administration, it is difficult to quantify it in plasma.\textsuperscript{21} Therefore, quantifying its inactive metabolite (SR26334), which represents about 85% of circulating metabolites, is an indirect approach to determine the pharmacokinetics of clopidogrel.\textsuperscript{4,8,22} Moreover, SR26334 as well as clopidogrel could not be detected after oral administration of CNM at a dose less than 30 mg/kg of clopidogrel base in rats. The total plasma concentrations of SR26334 from the solid dispersion were significantly higher compared to that of CB and CNM powder (Fig. 7). CNM administration led to a lower total plasma concentration than did CB and the solid dispersion. In particular, the solid dispersion (2122.7±478.4 h·ng/mL) showed about a 4- and 1.6-fold higher AUC compared to that of CNM (527.3±147.4 h·ng/mL) and CB (1295.1±310.9 h·ng/mL), respectively (Table 2). The solid dispersion showed a significantly higher C\textsubscript{max} compared to that of CNM powder, but there were no significant differences in T\textsubscript{max}, t\textsubscript{1/2} and K\textsubscript{a}. The lower total plasma concentration of SR26334 from CNM was due to poor dissolution resulting from the poor solubility of the drug.\textsuperscript{21} On the other hand, in this surface-modified solid dispersion system, the surface of poorly water-soluble and hydrophobic CNM was covered with a hydrophilic polymer (HPMC) and surfactant (Tween 80), transforming it into a hydrophilic surface.\textsuperscript{6,8} Furthermore, this hydrophilic surface could facilitate the solubilization and dissolution of the drug from this solid dispersion. Thus, the high plasma concentration and bioavailability of the drug from this solid dispersion compared to that of CNM might be related to the enhanced drug solubility and dissolution.\textsuperscript{19,23,24} The pharmacokinetic study revealed that this solid dispersion significantly improved the oral bioavailability of the drug compared to that of CB and CNM.

**CONCLUSION**

Taken together, this solid dispersion system prepared with water, HPMC and Tween 80 can be used to enhance the bioavailability of CNM as well as to solve the stability problem of CB.

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

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