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Improvement of dissolution and absorption properties of poorly water-soluble drug by preparing spray-dried powders with α-glucosyl hesperidin

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ABSTRACT

The feasibility of α-glucosyl hesperidin (Hsp-G) to improve the dissolution and bioavailability of poorly water-soluble drug was investigated. A spray-dried powder (SDP) of Hsp-G and flurbiprofen (FP), an acidic drug (pK_a = 3.78) with low water solubility, was prepared by a spray-drying method. Powder X-ray diffraction analysis revealed the conversion of FP from the crystal to the amorphous form when dispersed in Hsp-G. The SDPs of FP/Hsp-G resulted in pronounced improvement in both the dissolution rate and solubility of FP. The apparent solubility of FP in hydrochloric acid solution (pH 1.2) was improved by 10-fold more than untreated FP crystals when prepared as SDPs in Hsp-G. The bioavailability of FP from the prepared SDPs was evaluated in vivo after oral administration to rats, in comparison with the untreated FP crystals. The results revealed 2.5- and 2.8-fold improvement in the C_{max} and AUC values, respectively, after oral administration of the SDPs of FP/Hsp-G. In conclusion, Hsp-G is a potentially safe material to enhance the dissolution and absorption of poorly water-soluble drugs.

1. Introduction

The oral route is the most desirable for drug administration due to its convenience and good patient compliance. When a drug is absorbed from the intestine, it must be dissolved in gastric and intestinal fluids. Recently, the beginnings of many new drugs with good pharmacological promise have been generated by technological innovation of combinatorial chemistry and high-throughput screening. However, the seeds of many of the new drugs discovered by those techniques are poorly water-soluble. Various techniques have been used to enhance dissolution rates in such cases, including the use of surfactants (Sheng et al., 2006), polymorphs (Shah et al., 1999), drug micronization (Dong et al., 2009), and solid dispersion (Biswal et al., 2008). Solid dispersion is widely used to generate particles because it can produce a solid dosage form in an amorphous state or in a monomolecular dispersed state of the drug. The improvement of drug dissolution from solid dispersion is attributed to drug particle size reduction, a possible solubilization effect of the carrier, and specific molecular interactions between the drug and polymer (Karavas et al., 2007; Leuner and Dressman, 2000; Sethia and Squillante, 2003). In general, solid dispersion is prepared with a water-soluble polymer, such as polyethylene glycol (Ahuja et al., 2007; Newa et al., 2008) or polyvinylpyrrolidone (Ahuja et al., 2007; Gupta and Bansal, 2005) as a carrier, to disperse the drug molecules in the polymer matrix. In addition, the sugars of mannitol, lactose, and so on were also used as carriers to disperse the drug (Arias et al., 1994; Deepti et al., 2007). The spray-drying technique is a useful method to obtain spherical particles of small size and close distribution. Moreover, this method has also been reported to have the advantage of producing a solid dispersion in a one-step process (Yang et al., 2007).

Functional food additives are one of the useful candidates for preparing spray-dried powders (SDPs), since those materials are relatively safe and inexpensive. Among them, transglycosylated food additives are attractive materials for new pharmaceutical excipients. We focused on α-glucosyl hesperidin (Hsp-G), especially for a mono-transglycosylated Hsp-G. Hesperidin, an abundant flavonoid in citrus fruits, is well known as vitamin P. This compound is reported to have significant anti-inflammatory, hypotensive, and analgesic effects (Gang et al., 2001). However, the applicability of hesperidin itself as a preventive medicine is limited due to its extremely low solubility in water. Its solubility was greatly improved when it was transglycosylated with cyclomaltodextrin glucanotransferase (Kometani et al., 1996, 1999, 2008). The transglycosylation of hesperidin, hesperidin glycosides, led to more than 300 times higher solubility than original hesperidin. We previously reported that the SDPs of naringenin, a hydrophobic food ingredient, showed dramatically improved solubility when it was prepared with Hsp-G (Tozuka et al., 2010). The SDPs of naringenin/Hsp-G resulted in 60-fold improvement in apparent solubility.

The possibility of applying Hsp-G to pharmaceutical additives has not been reported so far. The aim of the present study was to estimate the effect of the formation of SDPs of FP/Hsp-G on the

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improvement of dissolution and absorption properties of flurbiprofen (FP). Flurbiprofen was used as a model of a poorly water-soluble drug. The particles of FP/Hsp-G by the spray-drying method were studied. The physicochemical properties of SDPs were estimated by scanning electron microscopy (SEM) and powder X-ray diffractometry (PXRD). The dissolution profile of FP from the SDPs of FP/Hsp-G was compared to that with a water-soluble polymer. The absorption amount of FP after the oral administration of SDPs FP/Hsp-G to rats was compared to that of the untreated FP and to that after a physical mixture (PM) of FP/Hsp-G.

2. Materials and methods

2.1. Materials

Flurbiprofen (FP) was purchased from Tokyo Kasei Co. and used without further purification. α-Glucosyl hesperidin (Hsp-G: α-G hesperidin PAT) was a gift from Ezaki Glico Co. Hydroxypropylmethylcellulose (HPMC: Metolose 60SH-03) was a gift from Shin-Etsu Chemical Co. All other chemicals and solvents were of reagent grade. The chemical structure of Hsp-G is depicted in Fig. 6.

2.2. Preparation of spray-dried powders

Spray-dried powders (SDPs) of FP/Hsp-G or FP/HPMC were prepared using the spray-drying method. To prepare particles by the spray-drying method, 500 mg of FP and 5 g of Hsp-G or HPMC were dissolved in ethanol/water solution (8:2 v/v). This solution was fed to a spray dryer (GS31; Yamato, Japan) at rate of 10 mL/min and sprayed into the chamber from a nozzle with a diameter of 406 μm at a pressure of 0.13 MPa. The inlet and outlet temperatures of the drying chamber were maintained at 120 and 70 °C, respectively. All SDPs were dried in a dessicator with blue silica gel under reduced pressure for 1 day before their physicochemical properties were tested.

2.3. Physicochemical properties of SDPs

FP and Hsp-G (weight ratio of 1:10 (w/w)) were physically mixed in a glass vial using a vortex mixer for 5 min. Particle sizes of SDPs were measured by a laser diffraction size analyzer (LDSA-2400A; Tonichi-Computer, Japan) using a dispersing-in-air method (air pressure: 3.0 kgf/cm^2). The particle shapes were observed by scanning electron microscopy (JSM-T330A; Nihon Denshi, Japan). Prior to examination, the samples were mounted onto metal stubs and were sputtered with a thin layer of gold under vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 kV. The crystalline form of FP in SDPs was measured by the powder X-ray diffraction method (RAD-IC; Rigaku Denki, Japan). The scanning rate was 4°/min over a 2θ range of 5–30°.

2.4. Dissolution test

A dissolution test for the commercial FP powder and SDPs was carried out according to the Japanese pharmacopoeia (XV). Each prepared sample or the commercial drug powder (50 mg) was added to 900 mL of distilled water, JP first fluid (hydrochloric acid solution; pH 1.2) or JP second fluid (phosphate buffer solution; pH 6.8) at a temperature of 37 ± 0.5 °C, with paddle stirring at a rotation speed of 50 rpm. Three-milliliter samples were withdrawn at specific time intervals and filtered through a 0.2 μm filter. The concentration of FP was determined by HPLC.

2.5. Measurement of surface tension

Surface tension was measured by an online tensiometer, SITA Science Line t60 (SITA Messtechnik GmbH, Dresden, Germany). This tensiometer measures the whole dynamic ranges of measuring tasks of surface tension by measuring bubble pressure. In this study, a long bubble lifetime (1000 s) was selected to measure a semi-static condition in order to detect low concentrations of additives. Triplicated measurements were done for each experiment under conditions controlled at 37.0 °C. Ultrapure water was used for this experiment (Milli-Q® Academic A10, Millipore, Bedford, MA, USA).

2.6. Animal study

Sprague–Dawley male rats (9 weeks; 200–220 g; Japan SLC Inc., Shizuoka, Japan) were used. The rats were fasted for 1 day before the experiments and were anesthetized using diethyl ether. SDPs were orally administered (2 mg/kg FP) using an oral dosing syringe after dispersion in distilled water. Blood samples (600 μL) were taken from a jugular vein at 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 12.0 h after administration. Plasma was obtained from the blood samples by centrifugation for 10 min at 10,000 rpm. The 400 μL of ethanol was added to 100 μL of plasma. The mixture was vortexed and centrifuged at 10,000 rpm for 10 min to separate the plasma proteins. The supernatant was evaporated to dryness. The residue was dissolved in 100 μL of ethanol. The FP concentration in 20 μL of solution was measured by HPLC under the following conditions: pump, Jasco-880-PU; detector, Jasco-875; integrator, Jasco-807-IT; column, COSMOSIL 5C$_{18}$-MS-II (4.6 mm φ × 150 mm; Nacalai Tesque, Tokyo, Japan); column temperature, 40 °C; wavelength, 254 nm; flow rate, 1.0 mL/min. The area under the plasma concentration–time curve (AUC) was determined by the trapezoidal method. All experiments were approved and monitored by the Institutional Animal Care and Use Committee of Gifu Pharmaceutical University.

2.7. HPLC assay

A PU-980 was used to analyze the FP concentration. In the HPLC assay, a COSMOSIL 5C$_{18}$-MS-II column (4.6 mm φ × 150 mm; Nacalai Tesque, Tokyo, Japan) was used. The mobile phase consisted of 80% (v/v) methanol, 20% (v/v) water and 1% (v/v) 1 M acetic acid. The flow rate was controlled at 0.6 mL/min with 20 μL of injection volume. The FP was eluted at 40 °C and quantitated at a wavelength of 254 nm.

3. Results and discussion

A SDP of FP, an acidic drug (pK_a = 3.78) with low water solubility of 31.7 μg/mL at 27 °C (Govindarajan and Nagarsenker, 2005), was prepared by the spray-drying method with Hsp-G or HPMC. The FP contents in the SDPs of FP/Hsp-G and FP/HPMC were 8.4 ± 0.1% and 10.8 ± 0.3%, respectively, as compared to a theoretical content of 9.1%. The SDPs of FP/HPMC, a solid dispersion system with hydrophilic polymer, in order to compare the physicochemical properties and dissolution profile of FP/Hsp-G system. Although the amount of FP decreased slightly during the spray-drying process, FP molecules may be dispersed homogeneously in the presence of Hsp-G. The particle size and morphology of FP crystals, Hsp-G powder, physical mixture (PM) of FP/Hsp-G and SDPs of FP/Hsp-G were characterized by a laser diffraction size analyzer and SEM, as shown in Table 1 and Fig. 1, respectively. The FP crystals and Hsp-G powder showed irregularly shaped particles with a relatively wide particle size distribution, whilst the SEM images of SDPs of FP/Hsp-G show spherical aggregates with an average particle size of about 3 μm.

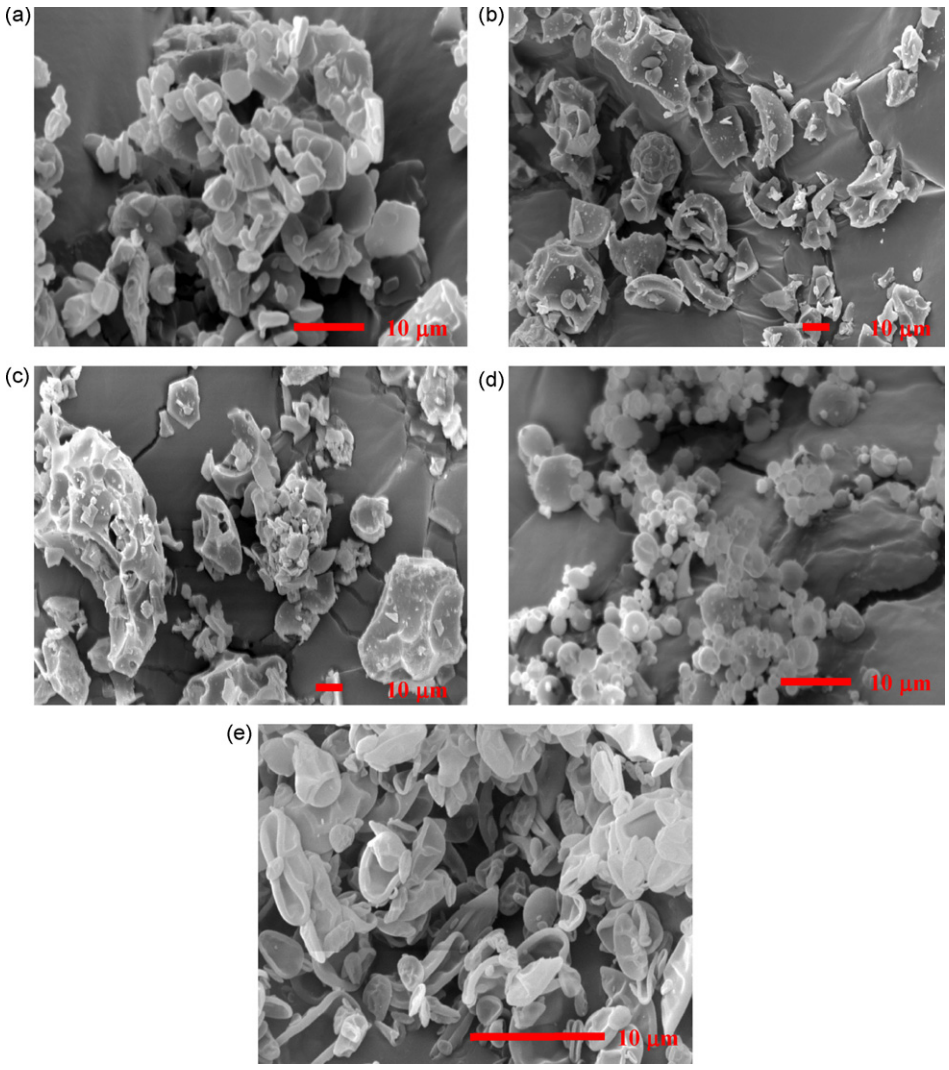

Fig. 1. SEM photographs of SDPs: (a) FP crystals, (b) Hsp-G powder, (c) PM of FP/Hsp-G(1/10), (d) SDPs of FP/Hsp-G(1/10), and (e) SDPs of FP/HPMC(1/10).

A comprehensive theoretical description of particle formation during spray drying has not been published. The micro-droplet drying process proceeds through nonequilibrium states where material properties are frequently unknown and experimentally difficult to access (Reinhard, 2008). Although the process condition affects the powder shape of the obtained sample, it was easy for SDPs to make spherical powders with a good content uniformity (Tajber et al., 2009).

The crystalline properties of FP in the different samples were evaluated by PXRD analysis. The characteristic crystalline peaks of FP were detected at 2θ values of 6.8° and 21.5°, as seen in the untreated FP and PM of FP/Hsp-G in Fig. 2. The PM of FP/Hsp-G showed a reduction in the intensity of the characteristic peaks of FD due to the dilution effect of Hsp-G. However, the diffraction peaks remained as a superimposed X-ray diffraction pattern of FP crystal and Hsp-G. SDPs of FP/Hsp-G and FP/HPMC showed no characteristic crystalline peaks of FP crystals, indicating that the long-range ordered molecular arrangement of FP did not exist in the SDPs. FP

Table 1
Particle size distribution (μm) of FP crystals, Hsp-G, PM of FP/Hsp-G(1/10), SDPs of FP/Hsp-G(1/10) and SDPs of FP/HPMC(1/10).

	D_{10}	D_{50}	D_{90}
FP crystal	4.23	7.61	10.36
Hsp-G	5.06	10.87	18.94
PM of FP/Hsp-G(1/10)	4.55	8.23	11.06
SDPs of FP/Hsp-G(1/10)	1.35	2.87	4.36
SDPs of FP/HPMC(1/10)	3.05	5.45	8.25

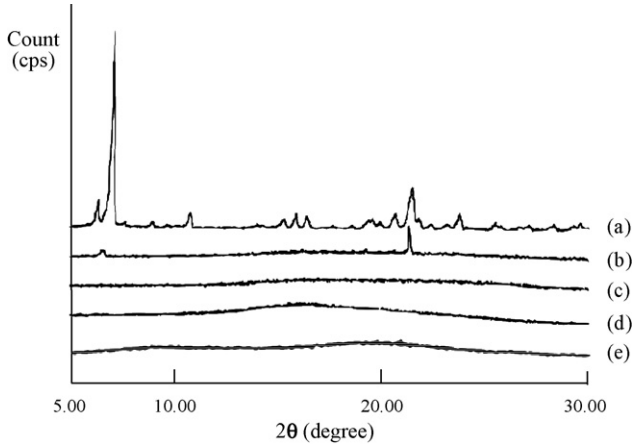

Fig. 2. Powder X-ray diffraction (PXRD) patterns of (a) FP crystal, (b) PM of FP/Hsp-G(1/10), (c) SDPs of FP/Hsp-G(1/10), (d) SDPs of FP/HPMC(1/10), and (e) Hsp-G powder.

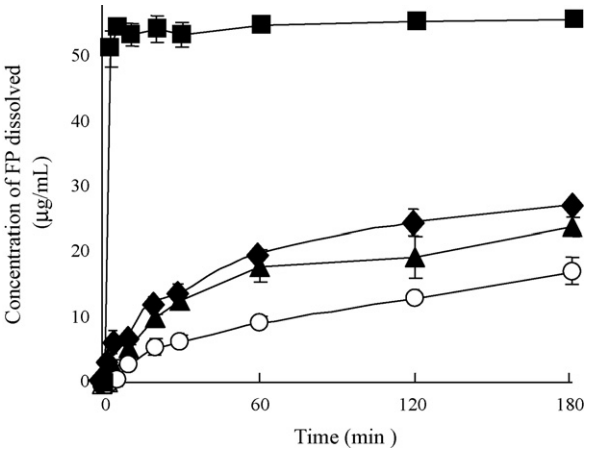

Fig. 3. Dissolution profiles of FP in distilled water: (○: untreated FP, ▲: PM of FP/Hsp-G(1/10), ■: SDPs of FP/Hsp-G(1/10), and ♦: SDPs of FP/HPMC(1/10)). Each point represents the mean ± S.D. ($n = 3$).

molecules were considered to exist in an amorphous form or in a monomolecular dispersed state in the SDPs. These results suggested that the existence of either Hsp-G or HPMC in the small droplets in the spray-drying process inhibited the crystal growth of FP and, as a result, FP existed in a condition of amorphous form or in a monomolecular dispersed state.

The solubility of FP was estimated as ca. 35 μg/mL in distilled water after incubation at 37 °C for 1 week. The solubility and dissolution rate of FP from the SDPs of FP/Hsp-G were evaluated in water and compared to those of the untreated FP, PM of FP/Hsp-G and SDPs of FP/HPMC (Fig. 3). The dissolution rate of untreated FP was considerably slow, with a maximum solubility of 17 μg/mL achieved after 3 h. In the cases of the PM of FP/Hsp-G and SDPs of FP/HPMC, the dissolution rate and solubility of FP were slightly improved compared to the case with the untreated drug. The solubility of FP from SDPs of FP/HPMC was 34.5 μg/mL after 24 h in dissolution test. On the other hand, SDPs of FP/Hsp-G showed rapid dissolution, with 100% of the drug dissolved within 5 min and a maximum solubility of more than 55 μg/mL. The aqueous solubility of a given solute in water typically depends on the temperature and pH of the medium, therefore the solubility of the drug is constant at a given temperature and pH. In our experiments, the solubility of FP prepared as SDPs of FP/Hsp-G showed a remarkable increase compared to that of the untreated drug in water at 37 °C.

With respect to drug solubility, at least two factors contributed to the improvement seen in Fig. 3. First is the change in the physical form of the drug from the crystalline to the amorphous form, and second is to form solid dispersion. For the solubilization of a solid solute, a first major hurdle to overcome is the disruption of crystal packing. A crystalline solid possesses relatively higher crystal packing energy than an amorphous solid. Therefore, an amorphous solid has low packing energy and no long-range order of molecular packing, indicating higher solubility than a crystalline solid (Kim et al., 2008). To make a solid dispersion, a solid dispersion with a water-soluble polymer, such as PVP, formed a water-soluble complex between the polymer and active substance and resulted in the increase in the solubility of the drug (Garekani et al., 2003). Although FP crystals had an amorphous form in the spray-dried system with HPMC in our report, the dissolution amount of FP from SDPs of FP/HPMC was dramatically lower than that with Hsp-G. This result indicates that, in the case of FP, changing the physical form of the drug from the crystalline to the amorphous form and utilization of a spray-drying system had little impact on the solubility of FP. A plausible explanation for a significant enhancement of apparent solubility of FP may be an existence specific structure

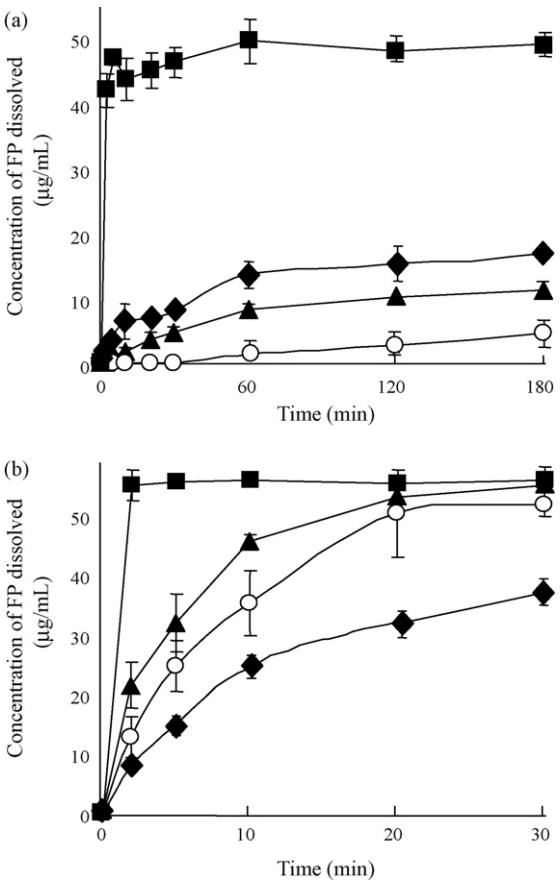

Fig. 4. Dissolution profiles of FP in (a) hydrochloric acid solution (pH 1.2) and (b) phosphate buffer solution (pH 6.8): (○: untreated FP, ▲: PM of FP/Hsp-G(1/10), ■: SDPs of FP/Hsp-G(1/10), and ♦: SDPs of FP/HPMC(1/10)). Each point represents the mean ± S.D. ($n = 3$).

of FP and Hsp-G in aqueous medium, by which FP was existed and solubilized in the special structure.

These results are in accordance with our previously published data on the enhancement effect of Hsp-G on the solubility of naringenin (Tozuka et al., 2010). We have shown that the SDPs of naringenin/Hsp-G have resulted in a dramatic increase in naringenin solubility when compared to SDPs of naringenin/HPMC. In addition, a direct relationship between drug solubility and the ratio of Hsp-G was observed. The suggested mechanism for this improvement in drug solubility may be explained by a specific molecular interaction, a micelle-like or clustered structure in which naringenin was incorporated with Hsp-G molecules. For further confirmation of the solubility enhancement effect of Hsp-G, we investigated the solubility of FP as shown in Fig. 4. FP is an acidic drug with a pK_a value of 3.78, so similar to other weakly acidic drugs, it has very low solubility in acidic media. When the FP was prepared as a SDPs of FP/Hsp-G the solubility of FP in hydrochloric acid solution (pH 1.2) was improved by 10-fold as compared to the untreated FP crystals. This result suggests that the solubilization potential of Hsp-G is not dependent on the pH of the medium. Furthermore, SDPs of FP/Hsp-G dissolved rapidly in phosphate buffer solution (pH 6.8) in comparison with untreated FP, PM of FP/Hsp-G, and SDPs of FP/HPMC. The SDPs of FP/Hsp-G resulted in pronounced improvements in both the dissolution rate and solubility of FP.

To further illustrate the mechanism of the solubility-enhancing effect of Hsp-G, we studied the interface properties of Hsp-G solution as a function of concentration. Fig. 5 shows the values of surface tension of various Hsp-G concentrations by the maximum bubble pressure method. The surface tension values of aqueous Hsp-G

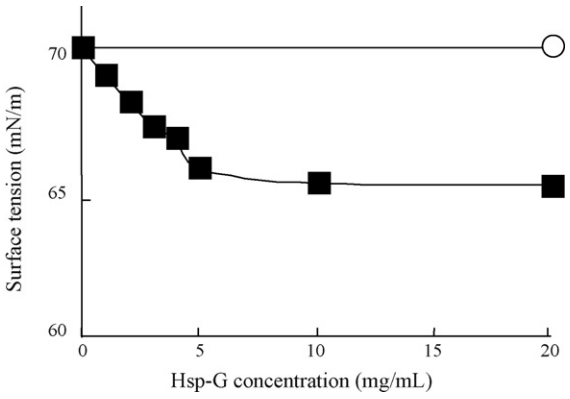

Fig. 5. Changes in surface tension to concentration of Hsp-G (○: distilled water and ■: Hsp-G).

solution were found to decrease when the concentration of Hsp-G was increased, indicating surface activity at the water–air interface. Fig. 6 illustrates the suggested solubility-enhancing mechanism of Hsp-G. Although the specific structure should be characterized in greater detail, at least the surface activity of Hsp-G in water contributed to the solubility enhancement. As shown in the chemical structure in Fig. 6, the molecular structure of Hsp-G is composed mainly of two parts: the hydrophilic part of the sugar portion and the hydrophobic part of the hesperetin portion. With respect to the proposed mechanism, aggregations of the hydrophobic domain of Hsp-G molecules can create a micro-environment suitable for the entrapment and solubilization of hydrophobic drug molecules.

The samples for oral administration were prepared by suspension in distilled water. The solubility of samples of untreated FP, the PM of FP/Hsp-G, and SDPs of FP/Hsp-G was about 25, 32, and 123 μg/mL, respectively, indicating that about 25% of FP in the suspension prepared for SDPs was solubilized. Fig. 7 shows the plasma concentration–time profiles of FP in rats after oral administration of untreated FP, the PM of FP/Hsp-G, and SDPs of FP/Hsp-G. The maximum drug concentration (C_{max}) of untreated FP and the PM of FP/Hsp-G was 3.73 ± 0.43 and 4.81 ± 0.23 μg/mL, respectively, at 1 h after oral administration. Meanwhile, the C_{max} of SDPs of FP/Hsp-G was 10.22 ± 0.14 μg/mL at a 0.5 h after oral administration and was obviously higher than that of untreated FP and the PM of FP/Hsp-G. The AUC up to 12 h for untreated FP, the PM of FP/Hsp-G, and SDPs of FP/Hsp-G was 22.06 ± 2.54, 32.09 ± 3.98, and 62.65 ± 2.82 μg h/mL, respectively (Fig. 8). The area under the curve (AUC) of the SDPs of FP/Hsp-G was 2.8-fold that of the untreated FP, suggesting that it is possible to improve the dissolution and oral absorption of water-insoluble FP by preparing SDPs using Hsp-G.

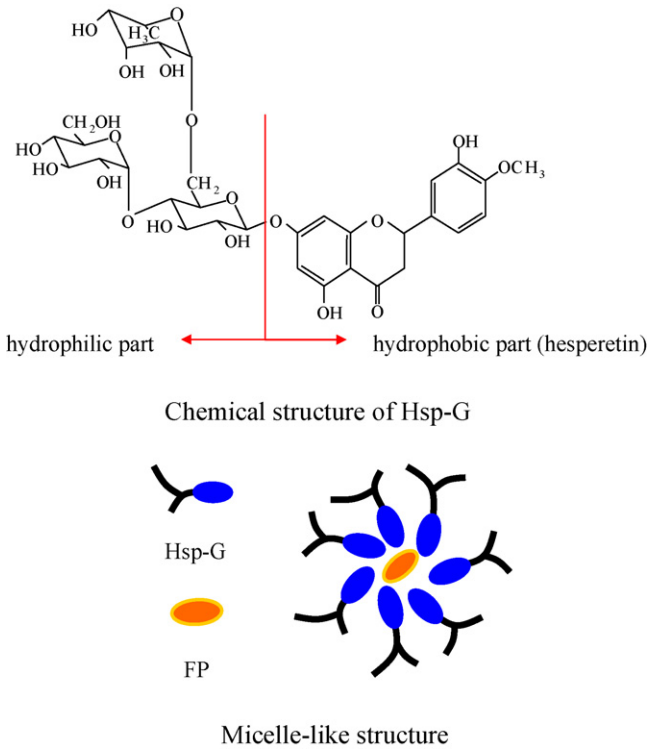

Fig. 6. Schematic representation of the structures formed in aqueous solution: a specific interaction among FP and Hsp-G molecules may indicate a significant solubility-enhancing effect of FP.

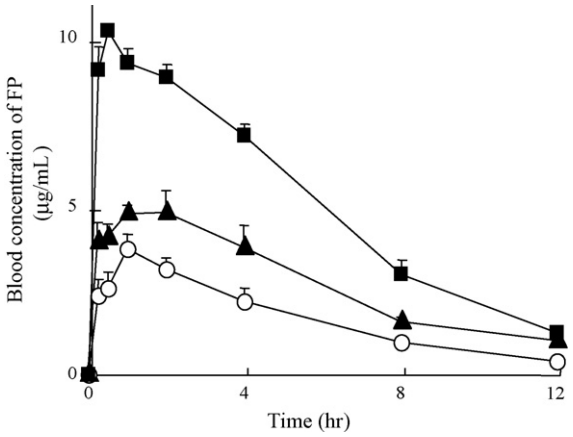

Fig. 7. Plasma concentration–time profiles of FP in rats after oral administration: untreated FP and SDPs: (○: untreated FP, ▲: PM of FP/Hsp-G(1/10), and ■: SDPs of FP/Hsp-G(1/10)). Each point represents the mean ± S.E. (n = 6).

The Biopharmaceutics Classification System (BCS), published by the U.S. Food and Drug Administration, provides guidelines for predicting intestinal drug absorption and classifies FP into Class II (Cirri et al., 2005). The features of Class II drugs are high permeability and low solubility, so the bioavailability of those products is limited by their dissolution. Mizoe et al. (2007) reported that FP-containing microparticles prepared by the four-fluid nozzle-spray drier enhance the dissolution and absorption of FP. In vitro disso-

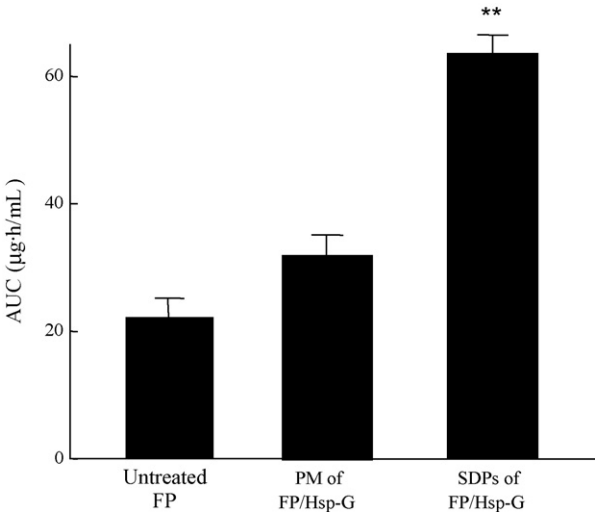

Fig. 8. Area under the plasma concentration–time curve (AUC) values of untreated FP and SDPs of FP/Hsp-G during 12 h after oral administration into rats. Each point represents the mean ± S.E. (n = 6). $^{**}p < 0.01$: significantly different from untreated FP.

lution test of SDPs of FP/Hsp-G showed more rapid dissolution and higher solubility than untreated FP and PM of FP/Hsp-G in distilled water, hydrochloric acid solution (pH 1.2), and phosphate buffer solution (pH 6.8). The increase in absorption would be attributed to drug dissolution in the small intestine, and a good correlation between the in vivo bioavailability and the in vitro dissolution can be found.

4. Conclusions

The in vitro dissolution properties of FP from SDPs of FP/Hsp-G and the in vivo studies of plasma concentrations of FP in rats after oral administration were estimated. SDPs of FP/Hsp-G showed marked improvement of FP dissolution compared to untreated FP, PM of FP/Hsp-G, and SDPs with a frequently used hydrophilic polymer, HPMC. Those findings are shown in distilled water, hydrochloric acid solution (pH 1.2), and phosphate buffer solution (pH 6.8), indicating that the specific enhancement of dissolution behavior from the SDPs of FP/Hsp-G occurred regardless of pH differences in solution. When SDPs of FP/Hsp-G were administered to rats orally, the maximum plasma concentration and AUC of FP significantly increased compared to untreated FP and the PM of FP/Hsp-G. This result suggests that SDPs of FP/Hsp-G can improve both the dissolution and oral absorption profiles of water-insoluble FP molecules. Preparation of the SDPs of FP/Hsp-G would be a promising way to improve the dissolution and absorption of other drugs that have poor water solubility.

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