Role of Low-Substituted Hydroxypropylcellulose in Dissolution and Bioavailability of Novel Fine Granule System for Masking Bitter Taste

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Coated fine granules with water-insoluble film composed primarily of ethylcellulose, containing 20% of sparfloxacin (SPFX) and various amounts of low-substituted hydroxypropylcellulose (L-HPC) (0–52%) in the cores and which masked the bitter taste of SPFX, were orally administered to fasting rats to determine the effect of L-HPC on bioavailability.

The release of SPFX in water from four kinds of these coated fine granules containing 0, 25, 40 and 52% of L-HPC showed the pseudo first order kinetics, followed by the second phase, with refractive points between 0.25 and 0.5 h. The rate constant (Kc) up to 0.25 h increased with an increase in the amount of L-HPC in the core, and the rate constant (K2) in subsequent release (the second phase) was lower than Kc in each fine granule.

Areas under plasma concentration–time curves (AUC) of SPFX and the peak plasma SPFX levels (Cmax) after oral administration of coated fine granules lacking L-HPC to fasting rats were suppressed to one-eighth and one-ninth, respectively, of those obtained from the core granules that rapidly released SPFX. However, AUC and Cmax from the coated fine granules increased linearly with an increase in the amount of L-HPC in the cores, and nearly equaled those from the core fine granules when the content of L-HPC was 52%.

These results confirmed that the addition of L-HPC to the cores increases not only the dissolution rate but also the bioavailability of SPFX.

Keywords: sparfloxacin; coated fine granule; bioavailability; rat; low-substituted hydroxypropylcellulose

In a previous report,1) we described that a novel fine granule system containing sparfloxacin (SPFX), which has a bitter taste, showed excellent characteristics: masking the bitter taste and rapidly releasing SPFX. This particle system consists of cores containing SPFX and 52% of low-substituted hydroxypropylcellulose (L-HPC) as a highly water swellable polymer, and a water-insoluble film layer composed of ethylcellulose (EC), hydroxypropylmethylcellulose (HPMC), titanium dioxide and sucrose fatty acid ester (4:2:2:1, w/w) around the cores to mask the bitter taste of SPFX. The mechanism of dissolution of SPFX from the coated fine granules is speculated to be as follows: after a short lag time, the core expansion due to water intake enhanced by L-HPC cases sudden bursting of the film thus releasing SPFX. Also, we reported that the amount of L-HPC played an important role not in masking the bitter taste, but in the dissolution which increased with an increase in amount of L-HPC.

In the previous report,1) however, we did not touch on the question of whether such fine granules show a similar dissolution behavior in vivo to that in vitro depending upon the amount of L-HPC in the cores, because there are some differences in the physical and chemical environments between the in vitro dissolution test and the gastrointestinal tract: for example, the volume, viscosity and pH of the fluid, and the mechanical force of the paddle stirring and the gut motility which can influence the bursting of the coated fine granules.

We also reported2) that the gastric emptying time and the intestinal transit time of non-disintegrated granules in rats were similar to those in fasting humans.3–6) Also, an aqueous solution was reported to be immediately emptied from the stomach in fasting rats.7,8) Based on this information, rats were thought to be suitable as a model of human for evaluating the bioavailability of fine granules considering the movement of preparations and dissolution of drugs in the gastrointestinal tract.

In the present report, we will discuss the effect of amount of L-HPC in cores of SPFX fine granules on the dissolution behavior and bioavailability in fasting rats.

MATERIALS AND METHODS

Material SPFX and SPFX trihydrate (Dainippon Pharmaceutical Co., Ltd.) with a mean diameter of about 15 μm, as measured by the air-permeability method on a Specific Surface Area Meter, Model SS-100 (Shimadzu Seisakusho Co., Ltd.). L-HPC (LH31) and HPMC (3 cep) were purchased from Shin-Etsu Chemical Co., Ltd. EC (10 cps), sucrose stearate (SS, Kyoto Sugar Ester, S-770), hydroxypropylcellulose (HPC, HPC L), titanium dioxide and lactose were purchased from Dow Chemical Co., Ltd., Mitsubishi-Kasei Foods Corp., Co., Ltd., Nippon Soda Co., Ltd., Ishihara Sangyo Kaisha Co., Ltd., and B. V. Hollandscbe, respectively.

Test Preparations The test preparation formulas are shown in Table I. The preparation method was described in a previous report.1) First, SPFX and other additives of the core fine granules were mixed in a high speed mixer. Vertical Granulator VG-25 (Powrex Co., Ltd.), at 300 rpm for 1 min. Ethanol was then added to dissolve HPC as a binder under successive mixing of powders. After drying the wet granulated powders at 70°C for 12 h and sieving the dry granulated powders using sieves with 150–32 mesh, core fine granules were obtained. These granules were coated with film suspension dispersing additives in dichloromethane–ethanol (15:2, w/w) solution, using a Spir-a-Flow MFINI (Freund Industrial Co., Ltd.). Four kinds of coated fine granules (formulas No. 2—5 in Table I) showed better masking effect of bitter taste1) than the
core fine granules (Table I).

**Dissolution Test** The dissolution tests were carried out according to the JP XII paddle method, at 50 rpm in 900 ml distilled water at 37°C. The fine granules, obtained using sieves with 60–32 mesh and containing 50 mg of SPFX were tested. At appropriate time intervals, the test mediums were filtered (FM-45, pore size 0.45 μm, Fuji Film Co., Ltd.) and diluted with 0.1 N NaOH. Concentrations of SPFX in samples were determined spectrophotometrically at 291 nm.

**Differential Scanning Calorimetry (DSC) Analysis** was performed by DSC (TAS-1000, Rigaku Denki Co., Ltd.), at a heating rate of 10°C/min. Sample weight of the dried precipitates at 50°C for 12 h after 30 min in the dissolution test of coated fine granules containing 52% of L-HPC was 8 mg. Sample weight of SPFX and trihydrate were 2 mg.

**Animals** Male Wistar strain rats weighing approximately 200 g were used after 24 h of fasting and were allowed free movement in individual cages with a wire net floor after dosing in order to prevent coprophagy.

**Administration** Injections were prepared by dissolving 10 mg of SPFX in 10 ml of 0.02 N NaOH solution. A dose of 5 mg of SPFX/kg body weight was administered as an intravenous bolus injection through the right femoral vein under slight anesthesia with diethylether.

To administer preparations orally, an apparatus consisting of a syringe, a sonde, and a polyethylene tube (2 mm in diameter and 30 mm in length) for packing the test fine granules was used. The test fine granules, containing 10 mg of SPFX/kg body weight, were administered with 0.5 ml of water.

Blood samples of 0.6 ml were withdrawn at suitable intervals from the jugular vein through a needle syringe with slight diethylether anesthetizing just before hand. The blood samples were immediately centrifuged at 3000 rpm to obtain plasma, and assayed by the HPLC method.39

**Pharmacokinetic Analysis** The maximum plasma concentration (Cmax) and the time to reach Cmax (Tmax) were read from individual plasma concentration–time curves of SPFX. The area under plasma concentration–time curves (AUC0–∞) was calculated by the linear trapezoidal method and the mean residence time (MRT) was calculated by moment analysis. Absolute bioavailability (BA) was calculated from the following equation:

\[
BA(\%) = \frac{AUC_0-\infty (p.o.)}{dose (i.v.) - 100/AUC_0-\infty (p.o.)} \times \frac{dose (p.o.)}{dose (i.v.)}
\]

**Table I.** Formulas of Core and Coated Fine Granules

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<td>HPMC</td>
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<td>2.22</td>
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<td>1.11</td>
<td>1.11</td>
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<tr>
<td>Total</td>
<td>90</td>
<td>100</td>
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**Statistical Analysis** The pharmacokinetic parameters and the plasma concentrations were subjected to Student's t test or Cochran-Co test. Differences in p values of less than 0.05 were considered to be significant.

**RESULTS**

**Dissolution Profiles of Coated Fine Granules** Figure 1 shows the semi-log plots of dissolution of SPFX in water from four kinds of the coated fine granules containing 0, 25, 40, 52% of L-HPC and the core fine granules lacking L-HPC. SPFX was dissolved immediately from the core fine granules, and also dissolved from four kinds of the coated fine granules in biphasic pseudo-first order kinetics, of which refractive points were between 0.25 and 0.5 h. Their dissolution rate constants, K1 and K2, estimated from 0 to 0.25 h and from 0.5 to 1.5 h, respectively, are summarized in Table II. K1 values were increased with an increase of the amount of L-HPC in the cores, and K2 was lower than K1 in each fine granule. The DSC curve of the precipitates after 30 min in the dissolution test of the coated fine granules containing 52% L-HPC in Fig. 2 indicates the presence of the trihydrate.

**Bioavailability of SPFX from Coated Fine Granules** Plasma SPFX concentration–time curves after intravenous administration of SPFX in 0.02 N NaOH solution at a dose of 5 mg/kg and after oral administration of the core fine granules lacking L-HPC at a dose of 10 mg/kg to fasting rats are shown in Fig. 3(a); those after oral ad-

![Fig. 1. Pseudo First Order Dissolution Plot of SPFX from Core Fine Granules and Coated Fine Granules Containing Various Amounts of L-HPC in Cores](image-url)

**Table II.** Rate Constants of Dissolution from Coated Fine Granules

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<tr>
<td>K1 (h⁻¹)</td>
<td>0.25</td>
<td>1.95</td>
<td>4.71</td>
<td>8.42</td>
</tr>
<tr>
<td>K2 (h⁻¹)</td>
<td>0.09</td>
<td>0.36</td>
<td>0.32</td>
<td>0.11</td>
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K1; obtained between 0 and 0.25 h, K2; obtained between 0.5 and 1.5 h. Nos. are defined in Table I.
ministration of the coated fine granules containing 0, 25, 40 and 52% of L-HPC in the cores at a dose of 10 mg/kg to fasting rats are shown in Fig. 3(b). Plasma concentration-time curves after intravenous administration were described using a two compartment model, and the mean elimination rate constant and the volume of distribution were 0.262 h⁻¹ and 3.28 l/kg, respectively. The plasma SPFX concentrations after oral administration of the coated fine granules increased with an increase in the amount of L-HPC in the core and were nearly equal to those of the core fine granules when the L-HPC amount was 52%.

Pharmacokinetic parameters, $AUC_{0-\infty}$, $C_{\text{max}}$, $T_{\text{max}}$, $MRT_{0-\infty}$ and $B4$ of the coated fine granules containing L-HPC and the core fine granules lacking L-HPC are summarized in Table III. Figure 4(a), (b), (c) and (d) shows the relationship of $AUC$, $C_{\text{max}}$, $T_{\text{max}}$ and $MRT$ to the amount of L-HPC, respectively. As shown in Fig. 4(a) and (b), $AUC$ and $C_{\text{max}}$ obtained from the coated fine granules increased linearly with an increase in the amount of L-HPC in the cores. Their relationships are expressed by the following equations with an eminence coefficient of correlation:

$$AUC (\mu g/ml\cdot h) = 0.544 + 0.082 \cdot A \quad (r = 0.9408)$$

$$C_{\text{max}} (\mu g/ml) = 0.086 + 0.018 \cdot A \quad (r = 0.9006)$$

$A$ (%); amount of L-HPC

There were significant differences in $AUC$ and $C_{\text{max}}$ among the coated finene granules. $AUC$ and $C_{\text{max}}$ values of those containing 0, 25 and 40% of L-HPC were significantly

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**Table III. Pharmacokinetic Parameters of Core and Coated Fine Granules**

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<th>Formula No.</th>
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<tr>
<td>$AUC_{0-\infty}$ (μg/ml·h)</td>
<td>4.90±0.14</td>
<td>6.65±0.12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.44±0.17&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.76±0.25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.97±0.46</td>
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<tr>
<td>$C_{\text{max}}$ (μg/ml)</td>
<td>1.32±0.12</td>
<td>0.15±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.44±0.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.74±0.08&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.09±0.12</td>
<td></td>
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<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.60±0.10</td>
<td>2.40±0.06&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.90±0.06&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.90±0.06&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.70±0.12</td>
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<tr>
<td>$MRT$ (h)</td>
<td>3.26±0.09</td>
<td>3.37±0.52&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.56±0.07&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.64±0.08&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.44±0.08</td>
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<tr>
<td>$B4$ (%&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>54.3±1.5</td>
<td>7.2±1.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27.0±1.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>41.7±2.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>55.1±5.1</td>
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Each value represents mean±S.E.  
<sup>a</sup> Absolute bioavailability: $AUC_{0-\infty}$, dose (i.v.):-100/$AUC_{0-\infty}$, dose (p.o.). Significant level between core fine granules (No. 1) vs. coated fine granules: b) p<0.01, c) p<0.05. Ncs. are defined in Table I.
lower \((p=0.05)\) than those of the core fine granules (formula No. 1).

\(T_{\text{max}}\) of the coated fine granules containing 52% of L-HPC was almost equal to those of the core fine granules, and faster than the coated fine granules containing less than 40% L-HPC. \(MRT\) of all coated fine granules depended little upon the amount of L-HPC; however, those of the coated fine granules lacking L-HPC were more varied.

Figure 5 shows that \(AUC\) increased linearly with an increase in the dissolved % of the coated fine granules in water at 30 min \((D 30 \text{ min})\). We also reported earlier\(^{11}\) that there was linear relation between \(D 30 \text{ min}\) and the amount of L-HPC.

**DISCUSSION**

In this study, we investigated the relationship between the amount of L-HPC in the core of the coated fine granules and the \emph{in vitro} dissolution profiles or the absorption in fasting rats.

In a previous paper, we showed scanning electron microscope photographs of coated fine granules containing 0, 25, 40 and 52% of L-HPC in the cores at 30 min in the dissolution test. It was found that the film surface of the coated fine granules lacking L-HPC hardly changed in water compared with that of the coated fine granules containing L-HPC. The degree of cracking and bursting of film were progressively enhanced with increase in the amount of L-HPC, and it was therefore thought that the increase of the dissolution rate constant, \(K_1\), with greater amount of L-HPC depended directly on the degree of cracking and bursting of the film layers. On the other hand, the lower dissolution rate constant, \(K_2\), from all the coated fine granules as observed after 0.5 h in the dissolution test, was thought to be due to the transformation of SPFX (solubility: > 1000 \(\mu\)g/ml) to trihydrate with lower solubility (about 100 \(\mu\)g/ml) at the early stage of the dissolution process (Fig. 2). It was suggested that this layer of the trihydrate covers the surface of particles of SPFX. Similarly, in the case of SPFX tablets that showed slower disintegration, the SPFX transformation to trihydrate was also observed in the dissolution process.\(^{10}\)

\(AUC\) of the coated fine granules lacking L-HPC was suppressed to about one-eighth that of the core fine granules which immediately released SPFX. This shows that the water-insoluble film on the cores to mask the bitter taste of SPFX is so hard that coated fine granules lacking L-HPC did not burst, released little SPFX, and passed through the small intestine where SPFX is mainly absorbed.\(^{11}\) \(AUC\) and \(C_{\text{max}}\) of the coated fine granules
increased almost linearly, with an increase in the amount of L-HPC in the cores as shown in Fig. 4(a) and (b), indicating that the bursting of the coated fine granules in the gastrointestinal tract was greatly enhanced, as observed in the dissolution test in vitro. Even in the coated fine granules which contained 40% of L-HPC in the cores the bursting was not complete, because their AUC and Cmax were significantly lower than those from the core fine granules.

Tmax of the coated fine granules containing less than 40% L-HPC had a tendency to prolong and to vary widely in contrast to those of the coated fine granules containing 52% of L-HPC and the core fine granules. This indicated that the bursting was not complete and the release of SPFX was neither rapid nor complete in the coated fine granules containing less than 40% L-HPC. While the amount of L-HPC in the cores did not greatly affect MRT, the variation of MRT was appreciably decreased by addition of L-HPC, as shown in Fig. 4d. Figure 5 and the previous findings1) indicate that there were close relations among the amounts of L-HPC, dissolution % (D30 min) and AUC.

The bioavailability of the coated fine granules containing 52% of L-HPC, on the other hand, was low in contrast to the dissolution % at 30 min. It is possible that this was not due to the bursting of these granules, but to other factors, i.e., the volume of fluid, the motility or the transit time in the gut. Because the bioavailability of the coated fine granules containing 52% of L-HPC in the core was almost equal to that of the core fine granules and was also equivalent to that after oral administration of aqueous SPFX suspension reported by Yamaguchi et al.9) the coated fine granules containing 52% of L-HPC were believed to burst immediately and dispersed in the gut.

We observed results in beagle dogs similar to those in rats, suggesting that the coated fine granules containing 52% of L-HPC almost perfectly burst in the stomach, regardless of animal species.

In conclusion, we determined the role of L-HPC in this novel coated fine granule system, without decreasing bioavailability irrespective of the water-insoluble film which masked the bitter taste. It is clear that the degree of burst of the coated fine granules in the gastrointestinal tract depends on the amount of L-HPC in a manner similar to that observed in the dissolution process in vitro.

REFERENCES