Efficacy and tissue distribution of DHP107, an oral paclitaxel formulation

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Abstract

Paclitaxel is indispensable in treating human cancers. Due to poor drug solubility and efflux systems in the gastrointestinal tract, peroral delivery of paclitaxel has been a significant challenge. We developed a mucoadhesive oral formulation (DHP107) that can directly and effectively deliver paclitaxel to intestinal endothelial cells without concomitant use of P-glycoprotein inhibitors. Here, we evaluated the tissue distribution of paclitaxel, the antitumor efficacy and the absorption mechanism of DHP107. DHP107, which contains 10 mg/mL of paclitaxel in a mixture of monoolein, tricaprylin, and Tween 80 was administered p.o. to female BALB/c mice at a 50 mg/kg dose. Diluted Taxol was administered via bolus tail-vein injection at 10 mg/kg as a control. Blood and tissue samples were harvested in various time points and analyzed by high-performance liquid chromatography. Tissue sections were observed using light microscopy after immunohistochemical and Oil Red O staining. By day 27, tumor volume after DHP107 and Taxol treatments was one-third of that in the untreated group. After p.o. administration, paclitaxel was widely distributed in various organs (Tmax = 2 h), especially liver, spleen, and lung. DHP107 was effectively absorbed through the intestinal lipid transport system. DHP107 changed spontaneously into <100-μm droplets and micelles in the intestine, which in turn adhered to mucop epithelial cells, were absorbed via lipid uptake mechanism, and formed lipid bodies in the epithelium. Paclitaxel in DHP107 was effectively absorbed through the gastrointestinal tract via lipid uptake mechanism and was distributed in various tissues. The detailed uptake mechanism is currently under investigation. [Mol Cancer Ther 2007;6(12):3239–47]

Introduction

Paclitaxel is a powerful prototypic taxane anticancer drug and is very effective in treating both early and advanced solid tumors including ovarian, breast, and non–small cell lung carcinomas (1–5). Paclitaxel is extremely insoluble in water, as well as in other vehicles commonly used in parenteral dosages, which has created significant problems in developing suitable injectable and infusion formulations for anticancer chemotherapy. The most widely marketed form of paclitaxel for i.v. infusion, Taxol, is formulated with an equivolume mixture of Cremophor EL and dehydrated alcohol (6). Frequent acute hypersensitivity reactions, however, characterized by dyspnea, flushing, rash, chest pain, tachycardia, hypotension, angioedema, and generalized urticaria, are a major side effect that is caused not by the active pharmaceutical ingredient but by the formulation (7). Paclitaxel is not bioavailable when administered p.o. due to overexpression of P-glycoprotein by intestinal cells and significant first-pass extraction by cytochrome P450–dependent processes (8, 9). The agent is, therefore, exclusively administered i.v., most commonly over a 3-h period (10). It is now well-recognized that alternative formulations are needed to allow better control of treatment toxicity and to avoid pharmacologic interactions such as those related to Cremophor EL use (11).

In an attempt to develop safer clinical paclitaxel formulations, we generated an efficient lipid-based oral paclitaxel formulation (DHP107). The formulation is composed of edible lipids and a Food and Drug Administration–approved emulsifier and does not include toxic excipients. Without concomitant administration of P-glycoprotein inhibitors, the oral bioavailability of paclitaxel was 14% to 20% in mice compared with the i.v. Taxol formulation. We also did antitumor efficacy studies in mice and showed that the tumor size of human non–small cell lung carcinoma was significantly reduced after p.o. administration of DHP107. In this article, we compared the tissue distribution of paclitaxel and antitumor efficacy after p.o. DHP107 delivery in animal models with those after i.v. Taxol administration. Using microscopic techniques, we also examined how this oily formulation is taken up in the intestine.

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Materials and Methods

Animals

Eight-week-old female BALB/c mice were purchased from Samtako BioKorea Co. and maintained for 1 week. Animal care and handling followed institutional guidelines (Korea Institute of Science and Technology). Mice were maintained with free access to food and water under a 12-h light/dark cycle.

Materials

Distilled monoolein (>90% pure, MG 19; RYLO) was purchased from Danisco Ingredients. Paclitaxel was obtained from Samyang Genex (Genexol). Cremophor EL, Tween 80, and tricaprylin were purchased from Sigma Chemical Co.

Drug Preparation and Administration

Paclitaxel was dissolved completely at 10 mg/mL in a mixture of monoolein, tricaprylin, and Tween 80 (1:0.5:0.3 by volume) by sonication for 20 s. This formulation will be referred to as DHP107. This oral paclitaxel formulation was a semisolid wax with a melting point of 33°C to 35°C, and therefore had to be warmed to body temperature before feeding. DHP107 was administered p.o. at 50 mg/kg with a blunt needle via the esophagus into the stomach. Diluted Taxol was prepared by dissolving paclitaxel in an equimolar mixture of Cremophor EL and ethanol at 6 mg/mL and diluting this mixture six times with saline solution. This preparation was administered via bolus tail vein injection at 10 mg/kg as a control. Blood and tissue samples were collected at various time points (n = 6) after drug administration and were stored at -70°C until high-performance liquid chromatography analysis.

Quantification of Paclitaxel

To determine the paclitaxel concentration, blood and tissue samples were prepared using the procedure described by Woo et al. (12) with slight modifications. In brief, blood samples (200 µL) were mixed with 800 µL of acetonitrile containing 10 µL of 100 µg/mL P-hydroxybenzoic acid n-butyl ester as an internal standard. After vortex-mixing, the mixture was centrifuged for 10 min at 14,000 rpm. The supernatant fraction (500 µL) was mixed with 500 µL of distilled water and filtered through a 0.2-µm PTFE syringe filter (Whatman, Inc.). The following tissues were also harvested: liver, spleen, kidney, heart, lung, stomach, intestine, and intestinal contents. Tissues were homogenized in five volumes of acetonitrile using a high-speed homogenizer (T-25-Ultra-Turrax; Janke & Kunkel GmbH & Co.). The homogenized tissues (990 µL) were mixed with 10 µL of internal standard solution and centrifuged for 30 min at 14,000 rpm. The supernatant fraction (400 µL) was mixed with 600 µL of distilled water and filtered through a 0.2-µm PTFE syringe filter (Whatman).

The acetonitrile extracts of blood and tissues were analyzed by high-performance liquid chromatography using a semimicro-HPLC system (SI-1; Shiseido, Japan). The column-switching system (Shiseido) was composed of an analytical column (5 µm, 2.5 × 35 mm; Capcell Pak C18 UG120), a precolumn (1.5 × 250 mm; Capcell Pak MG) and a concentration column (Capcell Pak C18 UG120, 5 µm, 2.0 × 35 mm). The UV detector was set at 227 nm with 0.001 absorbance units at full scale.

Bioavailability in Organs

Bioavailability is defined as the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed and becomes available at the site of drug action (13, 14). Bioavailability was calculated by comparing the blood paclitaxel concentrations after p.o. administration of DHP107 and i.v. injection of Taxol. To estimate the efficiency of drug absorption in different organs, we also define the bioavailability in organs as the area under the concentration-time curve, AUC: (AUCoral, organ / AUCi.v., organ) · (dosei.v. / dosecoral) × 100 in this article.

Tumor Experiment

EMT-6 murine mammary carcinoma cell (1 × 10⁴/mouse) suspension, purchased from American Type Culture Collection, was s.c. injected into the dorsal flank of 9-week-old BALB/c mice on day 0. DHP107 was administered p.o. at 50 mg/kg for three 5-day cycles separated by 2-day intervals. Mice i.v. administered diluted Taxol (10 mg/kg) and untreated mice were used as controls. Tumor volume was measured every 3 days after inoculation and calculated as follows: tumor volume = length × width × height × 0.5236 (12).

Immunohistochemistry

Formalin-fixed, OCT-embedded tissues were cut at 4-µm thickness, dried for 1 h at 60°C and washed twice with PBS for 15 min. Endogenous peroxidase activity was blocked with 0.1% (v/v) H₂O₂ in PBS for 10 min. Tissue samples were blocked with 5% skim milk in PBST (0.05% Tween 20 in PBS) for 1 h at room temperature and subsequently washed four times in PBST for 5 min. The samples were incubated for 1 h at room temperature with a 1:100 dilution of antitaxane rabbit antiserum/TA11 (primary antibody; Hawaii Biotech, Inc.) and washed four times in PBST for 5 min. Samples were then incubated with goat anti-rabbit IgG-horseradish peroxidase (1:1,000 dilution; Santa Cruz Biotechnology, Inc.) secondary antibody for 1 h at room temperature, and then washed four times in PBST for 5 min. Immunoreactivity was detected by incubation with 3,3’-diaminobenzidine substrate (DAKO) for 10 min. Samples were counterstained with hematoxylin for 10 s, cleared, and coverslipped using aqueous mounting medium (Sigma).

Photomicrographs of DHP107 in the Proximal Intestine

To observe how DHP107 interacts with intestinal fluids and tissues when ingested, intestines were harvested from mice at various time points after p.o. administration of DHP107. An oil-soluble red dye, Sudan IV, was also included in the 50 mg/kg DHP107 formulation for observation by optical microscopy. Rings of jejunum (0.1 mm of thickness) were transferred to glass slides for observation.

To visualize absorbed lipid droplets in the intestinal cells, intestines were obtained from mice given 50 mg/kg of DHP107 orally. Untreated intestine was used as a control. The jejunal segment was gently flushed with PBS and fixed in 10% buffered formalin for 24 h at room temperature.
Intestinal rings (1.5 cm) were cut from the fixed segments and frozen in cryoembedding media (OCT) for subsequent cryostat sectioning at 10 μm. Sections were applied to glass slides, incubated in Oil Red O solution (0.7% Oil Red O in propylene glycol) for 10 min at room temperature, washed with 85% propylene glycol and distilled water, and counterstained with hematoxylin.

The intestine was also visualized by transmission electron microscopy after p.o. DHP107 administration. For electron microscopy, tissues were postfixed in 1% osmium tetroxide, dehydrated in graded concentrations of acetone, infiltrated with the mixture of propylene oxide and Spurr’s resin and polymerized with 100% Spurr’s resin. Ultrathin sections cut using an ultramicrotome (MT-C, RMC; Boeckeler Instruments. Inc.) were stained with 2% uranyl acetate and lead citrate and examined with transmission electron microscope (JEM-1010, JEOL, Japan).

Results

Antitumor Activity of DHP107

In our previous investigation, we showed that the growth of human non–small cell lung carcinoma (NCI-H358) was significantly retarded by p.o. administration of DHP107 at a paclitaxel dose of 50 mg/kg.6 In the current study, we used a breast cancer cell line to test the antitumor efficacy of DHP107. The antitumor activity of oral DHP107 was evaluated by measuring the tumor volume in mice s.c. inoculated with EMT-6 murine mammary carcinoma cells (Fig. 1A). Mice administered diluted Taxol (10 mg/kg) i.v. and untreated mice were used as positive and negative controls, respectively. The treatment schedule for DHP107 and Taxol was 5-day cycles of once-a-day administration separated by 2-day intervals (q1d/C5). In untreated mice, the tumor volume increased slowly during the first 10 days, but was faster in the final 15 days after inoculation. When the tumor was treated with oral DHP107 (●), tumor volume was reduced to one-third of that in the negative control group (○) by day 27. This inhibitory effect by DHP107 was equivalent to that of i.v. Taxol administration at 10 mg/kg (C; n = 13 – 14). EMT-6 murine mammary tumor cells (1 x 104) were implanted s.c. (day 0). Drugs were administered daily for three 5-day cycles separated by 2-day intervals.

Plasma Concentration and Tissue Distribution of Paclitaxel from DHP107

To compare the efficacies of DHP107, we evaluated the plasma paclitaxel levels at several time points after p.o. administration of DHP107 (50 mg/kg) and i.v. injection of Taxol (10 mg/kg; Fig. 2). After Taxol administration, the peak plasma concentration (Cmax) was 23 μg/g at 1 min and declined rapidly with time. After DHP107 administration, Cmax was 2.2 μg/g at 2 h (Table 1) and declined to undetectable levels within 24 h. The oral paclitaxel bioavailability by DHP107 was calculated by comparing the blood paclitaxel concentrations after p.o. administration of DHP107 and after i.v. injection of Taxol; this was calculated as 22.7%.

Paclitaxel concentrations were also determined in the major organs (liver, spleen, kidney, heart, and lung) after p.o. DHP107 (50 mg/kg) and i.v. Taxol (10 mg/kg) administration (Fig. 2A). In the oral DHP107 group, paclitaxel was widely distributed in the tissues at higher concentrations than in the Taxol group at all time points except at 1 min. In the DHP107 group, the paclitaxel concentration in all of the organs investigated remained higher than the effective concentration (85.3 ng/mL) for 24 h (15). The time to reach maximum concentration (Tmax) was 2 h for p.o. DHP107 administration, except in the spleen (Tmax ≈ 4 h), and Cmax was highest in the liver (63.5 μg/g; Table 1). We visually confirmed the presence of paclitaxel in major tissues 2 h after p.o. DHP107 administration by immunohistochemical analysis (Fig. 2B). Prominent brown paclitaxel staining was observed in most tissues, except in heart tissues, compared with untreated controls.

Figure 1. Tumor volume (A) and weight (B) changes in BALB/c mice: negative control (○), p.o. DHP107 at 50 mg/kg (●), and i.v. Taxol at 10 mg/kg (C; n = 13 – 14). EMT-6 murine mammary tumor cells (1 x 104) were implanted s.c. (day 0). Drugs were administered daily for three 5-day cycles separated by 2-day intervals.

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After administration of DHP107 and Taxol at doses of 50 and 10 mg/kg, respectively, the AUC was comparable within the error range (Table 1). The bioavailability of paclitaxel in blood was 23%. Interestingly, the AUCs of paclitaxel by oral DHP107 in liver, spleen, kidney, heart and lung were two to five times higher than those of Taxol (Table 1). The absorption behavior of paclitaxel in spleen is particularly noteworthy. The oral bioavailability of paclitaxel in spleen was extremely high at 942%. The bioavailability of paclitaxel in liver was 108% for oral DHP107.

### Distribution of DHP107 in the Gastrointestinal Tract

Paclitaxel concentrations in the gastrointestinal tract were also determined after p.o. DHP107 and i.v. Taxol administrations at 50 and 10 mg/kg, respectively (Fig. 3A). We separated and quantified intestinal fluids from various gastrointestinal tissues. $C_{\text{max}}$ of paclitaxel in stomach tissue was extremely high at 942%. The bioavailability of paclitaxel in liver was 108% for oral DHP107.

### Table 1. Calculated AUC$_{0-24}$ of paclitaxel in blood and tissues ($n = 3$) after p.o. administration of 50 mg/kg DHP107 and i.v. administration of 10 mg/kg Taxol

<table>
<thead>
<tr>
<th></th>
<th>DHP107 (50 mg/kg)</th>
<th>Taxol (10 mg/kg)</th>
<th>Bioavailability in organs (%)</th>
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<tr>
<td></td>
<td>$T_{\text{max}}$ (h)</td>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>AUC$_{0-24}$ (µg·h/g)</td>
</tr>
<tr>
<td>Blood</td>
<td>2</td>
<td>2.2 ± 0.1*</td>
<td>10.4 ± 2.4</td>
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<tr>
<td>Liver</td>
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<td>63.5 ± 11.8</td>
<td>363.7 ± 80.0</td>
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<td>13.1 ± 2.7</td>
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<td>5.3 ± 1.3</td>
<td>36.4 ± 5.6</td>
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<tr>
<td>Lung</td>
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<td>Stomach</td>
<td>0.5</td>
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<td>11,978.9 ± 2,296.2</td>
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<tr>
<td>Jejunum</td>
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<td>78.4 ± 17.0</td>
<td>617.8 ± 102.0</td>
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<tr>
<td>Ileum</td>
<td>8</td>
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</tr>
<tr>
<td>Colon</td>
<td>24</td>
<td>113.1*</td>
<td>2,097.4 ± 145.4</td>
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*SD.

*Error could not be estimated ($n = 1$).
and fluid (content) was 908 and 1,728 μg/g at $T_{\text{max}} = 30$ min (Table 1). Approximately half of the total dose of paclitaxel remained in the stomach for up to 2 h following oral DHP107. After p.o. DHP107 administration, the time-dependent paclitaxel concentration profile in the jejunum was similar to that in blood; $C_{\text{max}}$ and $T_{\text{max}}$ in jejunum were 78 μg/g and 2 h, respectively, for oral DHP107 (Table 1). Paclitaxel existed in jejunum fluid at high concentrations for at least 8 h with $T_{\text{max}}$ at 4 h. On the other hand, $T_{\text{max}}$ was 8 h for ileum tissue and corresponding fluid. The paclitaxel concentrations in colon tissue and fluid increased with time for 24 h, thus $T_{\text{max}}$ could not be determined. In all of the intestinal tissues and their corresponding fluids, the paclitaxel concentration was lower for intravenous Taxol than for oral DHP107 by 30 to 2,000 times. We also visually identified paclitaxel in the gastrointestinal tract 2 h after p.o. DHP107 administration through immunohistochemical analysis (Fig. 3B). Following p.o. DHP107 administration, paclitaxel staining was observed in the mucosal and submucosal epithelium of the jejunum, but only in the mucosa of the ileum and colon.

**Fate of DHP107 in the Proximal Intestine**

The interaction of DHP107 with intestinal fluid was investigated *in vitro* by mixing DHP107 with artificial intestinal fluid with or without 5 mmol/L of bile salts, taurodeoxycholate (Fig. 4, top). To enhance the visibility of DHP107 and the resulting oil drops, a red-colored oil-soluble dye, Sudan IV, was added to the DHP107. Artificial intestinal fluid that did not contain bile salts was added to DHP107 at a 5:1 ratio by volume, and the mixture was shaken or vortexed to mimic peristalsis. When the mixture was shaken, big oil droplets (>100 μm) formed. On the other hand, when vortexed, smaller droplets (5–50 μm in diameter) were observed. In the presence of 5 mmol/L of bile salts, smaller oil droplets were formed by mere shaking although large droplets still existed. Vortexing in the presence of 5 mmol/L of bile salts further micronized the droplets in artificial intestinal fluid to >10 μm in diameter.

![Figure 3. Intraluminal kinetics of DHP107. A, the tissue and fluid concentrations of paclitaxel were determined at several points after p.o. administration of 50 mg/kg DHP107 (O) and i.v. Taxol at 10 mg/kg (●) in female BALB/c mice. B, immunohistochemistry of paclitaxel in intestinal tract tissues 2 h after p.o. DHP107 administration (50 mg/kg).](mct.aacrjournals.org)
We also observed the fate of DHP107 in jejunal lumen after p.o. DHP107 administration. BALB/c mice were given DHP107 containing Sudan IV and sacrificed 30 min, 1, 2, and 4 h post-dose to observe the jejunal lumen with an optical microscope (Fig. 4, bottom). At 30 min, DHP107 in the intestinal lumen existed as a lump of oil similar to its original state. At 1 h after p.o. administration, some of the DHP107 had become micronized particles (>5 μm), whereas some remained as lumps of oil spread throughout most of the jejunal tube. At 2 h post-dose, the oil lump had completely disappeared, and only oil particles that adhered to the epithelium remained in the intestine. Parts of these oil particles were further mixed with intestinal fluid, and possibly bile salts, to become turbid micellar solutions by 4 h after p.o. administration.

**Lipid Absorption in the Proximal Intestine**

To measure the degree of lipid absorption in intestine, intestinal tissue was collected after p.o. DHP107 administration (Fig. 5A). Fixed tissue sections were examined by light microscopy after Oil Red O and hematoxylin staining to observe lipid and tissue, respectively. In the fasted control group, the jejunum was stained purple, but did not show any red Oil Red O staining, indicating the absence of lipids in this tissue. When tissue was collected at 1 h after p.o. DHP107 administration, a vivid red color was localized on the margin of and along two distinct lines inside the epithelium. By 2 to 4 h, the red lipid staining was less localized in the villi, but still intense. From 8 to 24 h, the lipid droplets localized at the apical region of enterocytes decreased.

Lipid absorption was also evaluated by transmission electron microscopy in the proximal intestine 30 min after p.o. DHP107 administration (Fig. 5B). Unlike in the control group, large lipid droplets of various sizes (arrows) were present in the cytosol of enterocytes in the DHP107-treated group.

**Discussion**

Preparing cytotoxic agents for oral administration by synthesizing derivatives or different formulations has been in the forefront for the past several years (16). Oral treatment regimens offer the major advantage of convenience for the patient. Patients can take the medication by themselves with minimal medical supervision, no or short-term hospitalization, and minimal risk of infection (17–20). Moreover, oral chemotherapy allows the maintenance of an appropriate drug concentration in the systemic circulation to prolong the exposure of cancerous cells to the drug. This could increase the efficacy and decrease the side effects of anticancer drugs (21).

The solubility and permeability of a drug are the fundamental determinants of oral bioavailability (22). Unfortunately, most anticancer drugs, such as paclitaxel, are not orally bioavailable, i.e., not absorbable in the gastrointestinal tract. Paclitaxel has a low therapeutic index and is practically insoluble in water (23). The plasma concentration of paclitaxel must be above a threshold value of 0.1 μmol/L (equivalent to 85.3 ng/mL) to be pharmacologically active (15). Commercially available Taxol is currently formulated for systemic administration of paclitaxel in a mixture of ethanol and polyoxyethylated castor oil (Cremophor EL). Cremophor EL is primarily responsible
for drug-related hypersensitivity reactions rather than the drug itself (11). Therefore, oral formulations that could obviate the systemic exposure to Cremophor EL were prepared in the hope of achieving additional advantages over intravenous dosing, including elimination of the need for frequent visits to the outpatient clinic and easier chronic administration (24–26). However, paclitaxel was orally bioavailable only when coadministered with P-glycoprotein inhibitors (27).

Our lipid-based oral paclitaxel formulation, DHP107, is a semisolid paclitaxel formula that is orally bioavailable without P-glycoprotein inhibitors.7 DHP107 is composed of edible lipids and a Food and Drug Administration–approved emulsifier and does not include toxic excipients. We selected monoolein as the major ingredient due to its mucoadhesive property (28, 29). Because monoolein forms a very viscous gel and adheres to a small section of the intestine, it was necessary to decrease the viscosity of the formulation so that it would micronize into smaller particles and spread to larger portions of the intestinal tract. Tricaprylin and Tween 80 provided the best physical characteristics for this, and were therefore added as the other ingredients. We then evaluated antitumor efficacy in tumor-bearing mice after p.o. DHP107 administration. Tumor growth was significantly inhibited by p.o. DHP107 administration at 50 mg/kg, and this inhibitory effect was equivalent to that of Taxol injection at 10 mg/kg. Moreover, although mice in the group treated with repeated Taxol injections showed toxicity-related body weight loss, mice in the oral treatment group were healthy with slower weight gain than the control group. The animal antitumor study results suggest that DHP107 retained the therapeutic benefits of paclitaxel but eliminated the toxicities associated with intravenous Taxol.

After p.o. DHP107 administration and i.v. Taxol injection, we compared paclitaxel concentrations in blood and various organs at several time points. Paclitaxel levels in the blood stayed above the effective concentration for

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7 Submitted for publication.

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Figure 5. Accumulation of lipid in jejunal tissue after p.o. administration of 50 mg/kg DHP107 (A). Intestinal segments were fixed in paraformaldehyde and embedded in OCT. Frozen sections were stained with lipid-specific Oil Red O and with hematoxylin, and visualized by light microscopy. Lipid absorption in the intestine after p.o. administration of 50 mg/kg DHP107 (B). Intestinal absorptive cells for negative control and oral DHP107 group, 0.5 h after p.o. administration, were observed with transmission electron microscopy. Arrows, lipid bodies in the cytosol.
several hours after oral administration, and the time-dependent distribution profile of paclitaxel in most organs (liver, spleen, lung, kidney, gastrointestinal tract) was similar to that in the blood for oral DHP107. This study also showed that paclitaxel from DHP107, which does not contain P-glycoprotein inhibitor, was effectively absorbed in major tissues.

The presence of paclitaxel in major organs was also confirmed by immunohistochemistry. However, we could not find paclitaxel staining in either the heart or liver tissue following p.o. DHP107 administration. Rather, we observed paclitaxel staining inside blood vessels in the liver. This phenomenon may be caused by the overexpression of multidrug resistance and multidrug resistance-related proteins in the liver (30, 31). The elimination half-life was 2.78 and 0.55 h for 50 mg/kg of DHP107 and 10 mg/kg of Taxol, respectively. The finding that plasma and tissues concentrations of paclitaxel remained above the threshold value for several hours suggests that oral DHP107 could provide effective antitumor efficacy for various cancers.

After ingestion, DHP107 moved from the mouth to the trachea, stomach, and intestines as time progressed. Time-dependent changes in paclitaxel concentration in various parts of the gastrointestinal tract showed that \( T_{\text{max}} \) was 0.5, 2, 8, and >24 h for stomach, jejunum, ileum, and colon tissues, respectively. The half-emptying time of paclitaxel was ~4 h in the stomach. DHP107 stayed in the jejunum for >8 h. The prolonged gastric emptying and intestinal transit time probably contributed to the high bioavailability of DHP107. Previous studies have reported that the gastrointestinal absorption of orally administered drugs is determined by the permeability of the drug in the gastrointestinal mucosa as well as by the transit rate (residence time) in the gastrointestinal tract (32, 33). Photomicrographs of the jejunum after p.o. DHP107 administration showed lipid droplet formation and adhesion to the luminal surface of enterocytes for at least 8 h. The mucoadhesiveness of DHP107 might help increase the transit time and the permeability of the drug. In contrast, paclitaxel concentrations in the intestine and its fluid were low after i.v. Taxol administration, probably due to hepatobiliary excretion (34).

The physiologic processes of lipid digestion and absorption are likely relevant to this enhanced drug delivery because DHP107 is a lipid-based formulation. The lipid digestion and absorption processes, and their direct association with lymphatic transport of lipophilic drugs, have been reviewed extensively (35, 36). Among the proposed mechanisms for intestinal drug absorption, we have been reviewed extensively (35, 36). Among the proposed mechanisms for intestinal drug absorption, we have been reviewed extensively (35, 36).

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References
Molecular Cancer Therapeutics

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