Absorption profiles of an oral paclitaxel formulation, DHP107 with variable dosing intervals in mice

Yura Jang1, Yeong Woo Jo2, Hankoo Lee2, Hesson Chung1

1Korea Institute of Science and Technology, Seoul, 136-791, Korea; 2DAEHWA Pharm., Gangwon, 225-804, Korea
abc211@hanmail.net

ABSTRACT SUMMARY
The absorption of paclitaxel was evaluated after bid dosing of an oral paclitaxel formulation, DHP107 in mice. DHP107 was administered twice in 2, 4, 8 and 24-hour intervals at a dose of 50 mg/kg. While DHP107 was administered for the first dosing to the first group of mice, F109, a formulation without paclitaxel was administered to the other group. The AUCs of the second dosing were considerably smaller than those of the first in all cases, and were bigger for the F109 groups than the DHP107 groups. The decreased absorption could be due to mucoadhesiveness of the formulation and activation of P-glycoproteins.

INTRODUCTION
A lipid-based oral paclitaxel formulation, DHP107 is composed of monoolein, tricaprylin, tween 80 and paclitaxel1. Since the formulation was designed to be mucoadhesive, DHP107 adheres onto gastrointestinal tract, especially on the stomach and the upper intestine. In animal studies oral bioavailability of DHP107 was about 21% when compared to intravenous Taxol®. The antitumor efficacy at a dose of 50 mg/kg of oral DHP107 was similar to that at 10 mg/kg of Taxol®1. In clinical phase I study, single-dose oral treatment of DHP107 was shown to be safe and feasible with no dose limiting toxicity up to 600 mg/m² in patients with advanced solid tumors2.

In this study we conducted a pharmacokinetic study when DHP107 was administered two times at various intervals. Especially we focused on observing the effect of the first dosing on the absorption of the second to get an insight into the mechanism of absorption of DHP107. Since the formulation itself can influence the absorption of paclitaxel in the second, we also conducted experiments with a blank formulation, F109 instead of DHP107 for the first dosing.

EXPERIMENTAL METHODS

Animals
Female BALB/c mice, 6 to 8 week-old, were obtained from Nara Biotech (Korea) and were housed under a 12-hour light/dark cycle in a cage and given food and water ad libitum. All animals care and handling followed institutional guidelines of the Animal Care and Use Committee in Korea Institute of Science and Technology.

Materials
DHP107 was provided by DAEHWA Pharmaceutical (Gangwon, Korea). Distilled monoolein (RYLOTM MG 19, >90 % pure) was purchased from Danisco Ingredients (Copenhagen, Denmark). Tween 80 and Tricaprylin were obtained from Sigma Chemical Co.. Acetonitrile and methyl alcohol of HPLC grade were purchased from JT Baker (Phillipsburg, NJ, USA).

Drug administration
DHP107 containing 1 % (w/v) paclitaxel was orally administered to mice at a dosage of 50 mg/kg. F109, containing same components except for paclitaxel, was orally administered to other mice groups at an equal volume with DHP107. For the second dosing at 2, 4, 8 and 24 hour intervals, all mice were orally administered with DHP107 after the first oral dose of F109 or DHP107.

Samples preparation
Blood was collected at various time points (0.5, 1, 2, 4, 8, 12 and 24 hours) after each administration (n=5 per each sampling time). Plasma samples were stored at - 70 ºC until analysis.

LC MS/MS analysis
The LC-MS/MS system consisted of an Agilent 1100 series (Agilent Technologies, Waldbronn, Germany) and API3200 (AB Sciex, Toronto, Ontario, Canada). The analytical column was Waters XTrerra® MS C18 (3.5 µm, 2.1 mm × 50 mm). The mobile phase A was 5 mM ammonium formate (pH 6.0), and the mobile phase B was 90 % acetonitrile containing 5 mM ammonium formate (pH 6.0). The data acquisition was accomplished by Analyst® Software (Applied Biosystems). Pharmacokinetic analysis
The mean and SE of the five samples at each time point were calculated, and pharmacokinetic parameters were determined from the mean concentration data using WinNonLin® (Pharsight Corporation, Mountain View, CA, version 3.1) and KaleidaGraph 4.0 (Synergy Software, Reading, PA) program.
RESULTS AND DISCUSSION

Plasma paclitaxel concentration is shown in Figure 1 after bid dosing of oral DHP107. In all cases, \( C_{\text{max}} \) and AUC decreased considerably for the second dosing when compared to the first dosing. The second peak was not separated from the first in case of the 2-hour interval, but well separated for 4, 8 and 24-h intervals. \( T_{\text{max}} \) was 2 hours for the first dose, but was 1 hour after the second administration.

![Figure 1](image1.png)

**Figure 1** Plasma Paclitaxel concentration after DHP107 oral bid dosing at various time points

The AUCs for the second dosing of DHP107 were calculated and are shown in Figure 2. When F109 was given at the first, the absorption of paclitaxel for the second DHP107 dosing was considerably higher than when DHP107 was administered at the first in all time-interval cases. These results gave a suggestion that the activation of P-glycoprotein by absorbed paclitaxel could inhibit the absorption of paclitaxel in the second dose. The result that the expression of P-glycoprotein increased until 6 ~ 10 hours in the intestine and decreased with time (data not shown) could explain the lowest AUC for at an 8-hour interval of DHP107 bid dosage.

![Figure 2](image2.png)

**Figure 2** The AUCs of plasma paclitaxel after the second administration in F109 or DHP107 groups

CONCLUSIONS

The bid DHP107 dosing studies in mice showed that the absorption of the second dose of paclitaxel was inhibited by the activation of P-glycoprotein and mucoadhesiveness of the formulation. Also the time interval between the two doses may be an important factor for obtaining maximum absorption profile of paclitaxel in the clinical studies.

REFERENCES


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