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Research paper

# Enhanced paclitaxel bioavailability after oral administration of paclitaxel or prodrug to rats pretreated with quercetin

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**Abstract**

The aim of this study was to investigate the effect of quercetin on the bioavailability of paclitaxel after the oral administration of paclitaxel or a prodrug to rats pretreated with quercetin. Paclitaxel (40 mg/kg) and prodrug (280 mg/kg, 40 mg/kg as the paclitaxel) were administered orally to rats pretreated with quercetin (2, 10, 20 mg/kg). The plasma concentrations of paclitaxel pretreated with quercetin were increased significantly ($P < 0.01$, for paclitaxel; $P < 0.05$, for prodrug) compared to the control. The areas under the plasma concentration–time curve (AUC) and the peak concentrations ($C_{max}$) of paclitaxel pretreated with quercetin were significantly higher ($P < 0.01$) than the control. The half-life ($t_{1/2}$) and mean residence times were significantly ($P < 0.05$) longer compared to the control. The absolute bioavailability (AB%) of paclitaxel pretreated with quercetin was significantly higher ($P < 0.01$) than the control. The AUC of paclitaxel after administration of the prodrug to rats pretreated with quercetin was significantly ($P < 0.05$) higher than the prodrug control. The relative bioavailability of paclitaxel after administration of the prodrug to rats pretreated with quercetin was 1.25- to 2.02-fold higher than the prodrug control. The AB% of paclitaxel was increased significantly ($P < 0.05$) by quercetin from 8.0 to 10.1 and 16.2%. The bioavailability of paclitaxel administered as a prodrug with or without pretreatment of quercetin was remarkably higher than the control. AUC, AB% and $C_{max}$ of paclitaxel after administration of the paclitaxel or prodrug pretreated with quercetin for 3 days were much higher than those administered after 20 min. It might have resulted from the physicochemical properties of the prodrug, which is a water-soluble compound and passes through the gastrointestinal mucosa more easily than paclitaxel without obstruction of P-gp and cytochrome P-450 in the gastrointestinal mucosa. It seems that the development of oral paclitaxel preparations as a prodrug or with quercetin is feasible, which is more convenient than the i.v. dosage forms.


*Keywords:* Paclitaxel; Prodrug; Quercetin; Pharmacokinetic; Bioavailability; Pretreatment

## 1. Introduction

Paclitaxel (Taxol®) is an antineoplastic agent that is derived from the bark of the Pacific yew tree (*Taxus brevifolia*) [1]. In contrast to Vinca alkaloids, the anticancer action of taxol is that it inhibits cellular growth by promoting and stabilizing the microtubule assembly by a non-covalent interaction with tubulin, which blocks cell replication in the late $G_2$ mitotic phase of the cell cycle [2,3]. Because of its poor water solubility, paclitaxel is currently formulated as taxol and a mixture of polyoxyethyleneglycerol triricinoleate 35 (Cremophor EL) and dehydrated ethanol USP (1:1, v/v) for the i.v. dosage form. Cremephor EL itself is toxic and produces vasodilation, labored breathing, lethargy and hypotension when administered intravenously. One mediator of the hypersensitivity reactions is the endogenous histamine release, and prophylaxis to counteract the histaminergic mechanisms reduces the incidence of the hypersensitivity reactions [4]. Paclitaxel has been used to treat ovarian carcinoma, breast carcinoma, leukemia, melanoma, prostate carcinoma, etc., and has become particularly important in managing ovarian and breast carcinoma [5–8]. The oral administration of the paclitaxel is problematic as it has poor absorption due to the poor solubility and efflux pump function of the drug for

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the multidrug transporter P-glycoprotein (P-gp), which is present abundantly in the gastrointestinal tract. Thus, this drug is mainly used for i.v. administration [9].

Paclitaxel has a very large volume of distribution in the body, and is highly bound by plasma protein, primarily albumin (95–98%) [10]. In particular, it is much higher in disposition of the liver and bile than in the other tissues [11]. Less than 6–10% of administered paclitaxel is recovered as the unchanged drug in the urine of treated patients [10,12,13]. Paclitaxel is mainly metabolized through the liver and undergoes biliary excretion [14–17]. In humans, the total fecal excretion is approximately 70% of the paclitaxel dose, with 6α-hydroxypaclitaxel being the major metabolite [18].

In an attempt to develop safer formulations, many studies have been directed towards a new oral formulation. However, paclitaxel is very poorly absorbed when administered orally. Several studies have reported that the poor bioavailability of paclitaxel would result from the metabolism by enzymes or counter-transport processes by P-gp in the gut wall. It has been suggested that, in some cases the poor absorption of drugs after oral administration results from the activity of a multidrug transporter, a membrane-bound P-gp, which functions as an energy-dependent transporter or an efflux pump to decrease the intracellular accumulation of the drugs by extruding xenobiotics from the cell [9].

Flavonoids are regarded as a new class of chemosensitizers, which interact with both the cytosolic domains of P-gp and its ATP binding site [19]. It also has been reported to act as various CYP enzyme inhibitors or antioxidant agents [20].

Quercetin as a member of the flavonoids class, has been reported to possess the ability to inhibit the P-gp pump efflux [21]. It also has been reported that quercetin can inhibit CYP 3A, which is the main subfamily of the cytochrome P-450 that is responsible for metabolizing paclitaxel as 6α-hydroxytaxol [15]. In addition, it can competitively inhibit CYP 2A8, which induces the formation of 6α-hydroxytaxol [16].

This study introduces a water-soluble prodrug compound, 7-mPEG 5000-succinyloxymethyloxycarbonyl-paclitaxel, which combines a water-soluble polymer with paclitaxel [22]. It is rapidly hydrolyzed by an esterase to generate the physiologically active paclitaxel. The aim of this study was to investigate oral paclitaxel preparations, which will be more convenient than the i.v. dosage form, in an attempt to enhance the bioavailability of paclitaxel co-administered paclitaxel or a prodrug with quercetin orally in rats.

## 2. Materials and methods

### 2.1. Materials

Paclitaxel was purchased from Brystol-Myers Squibb Co. (NY, USA). Saline (0.9% NaCl injectable solution) was obtained from Choongwae Co. (Seoul, Korea). Acetonitrile, methanol, *tert*-butylmethylether were acquired from Merck Co. (Darmstadt, Germany). Quercetin and *n*-butyl *p*-hydroxybenzoate (butylparaben) were purchased from the Sigma Chemical Co. (St Louis, MO). Phosphoric acid was obtained from the Junsei Co. (Tokyo, Japan). The other chemicals were of reagent grade and were used without further purification. The apparatus used were a high-performance liquid chromatography system (HPLC, Waters 1515 isocratic HPLC Pump, Waters 717 plus autosampler, Waters 2487 Dual λ absorbance detector, Waters Co., Milford, MA), centrifugal evaporator (Rikakikai Co., Japan), a mechanical stirrer (Scientific Industries, USA), a centrifuge (Hanil Science Industrial Co., Korea), a micro-centrifuge (National Labnet, USA), a sonicator (Daihan Co., Korea), a refrigerated bath circulator and a rotamix (SeouLin Biosience, Korea).

### 2.2. Synthesis of prodrug

A water-soluble prodrug compound was obtained by introducing a new self-immolating linker that spontaneously decomposes into paclitaxel and a water-soluble polymer, and combines the water-soluble polymer with the resulting product. The prodrug compound is rapidly hydrolyzed by an esterase to generate the physiologically active paclitaxel [22]. The prodrug, 7-mPEG 5000-succinyloxymethyloxy-carbonyl-paclitaxel, was synthesized as follows-7-chloro-methyloxycarbonyl-paclitaxel (1.057 mmol) was dissolved in anhydrous benzene. Monomethoxypolyethyleneglycol 5000-succinate (1.057 mmol), sodium iodide (3.171 mmol), potassium carbonate (1.902 mmol) and 18-crown-6 ether (0.739 mmol) were mixed in the resulting solution. The mixture was stirred for 36 h under reflux and dried under reduced pressure to remove the benzene, and then dissolved in dichloromethane. The obtained material was filtered to remove the undissolved material. The organic layer was washed twice with water, the separated organic layer was dehydrated over anhydrous magnesium sulfate, dried under reduced pressure and recrystallized from isopropyl alcohol to obtain the solid material. The solid material was purified with HPLC for collection (Prep. HPLC) to a yield of 68%. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.39–3.38 (m, mPEG), 5.88 (d, 1H, $J = 5.85$ Hz, OCOO$CH_2$O), 5.71 (d, 1H, $J = 5.85$ Hz, OCOO$CH_2$O). A more detailed procedure will appear elsewhere [23–26].

### 2.3. Animal experiments and drug administration

Male Sprague-Dawley rats (270–300 g) were purchased from Dae Han Laboratory Animal Research and Co. (Choongbuk, Korea), and had free access to normal standard chow diet (Jae Il Chow, Korea) and tap water. Throughout the experiment, the animals were housed, four or five per cage, in laminar flow cages maintained at 22 ± 2 °C, 50–60% relative humidity, under a 12-h light–dark cycle. The animals were kept in these facilities for at least 1 week

before the experiment. This experiment was carried out in accordance with the 'Guiding Principles in the Use of Animals in Toxicology' adopted by the Society of Toxicology (USA) in July 1989 and revised in March 1999. The animal care committee in our institution (Chosun University) approved the present study.

Sprague-Dawley rats were fasted for at least 24 h prior to experiments and were given water freely. Each rat was anaesthetized with ether. The right femoral artery was cannulated with polyethylene tubing (PE-50, Intramedic, Clay Adams, NJ) for blood sampling. In the control group, paclitaxel suspension was prepared by adding paclitaxel (40 mg/kg) to distilled water (1.0 ml) containing tween80 (10 μl) and stirring for 1 h. The paclitaxel suspension or the prodrug solution (280 mg/kg dissolved in 1.0 ml distilled water) was administered orally to rats.

Paclitaxel dose (40 mg/kg) was chosen to keep plasma concentrations above the limit of detection [27] at 24 h. In pretreated group, quercetin (2, 10, 20 mg/kg) suspensions were prepared in distilled water (0.5 ml) containing tween80 (10 μl) and stirred for 1 h. The quercetin suspensions were administered orally to rats. Twenty minutes after quercetin suspension administration, or after quercetin suspension was administered for 3 days (bid 10 or 20 mg/kg), the paclitaxel suspension or the prodrug solution were administered to rats orally. Blood samples (0.6 ml) were withdrawn from the femoral artery 0, 0.25, 0.5, 1, 2, 3, 4, 8, 12 and 24 h, after the oral administration of the drug. The plasma samples were centrifuged at 5000 rev./min for 5 min. The plasmas were stored at −40 °C until the HPLC analysis.

### 2.4. HPLC assay

The plasma concentrations of paclitaxel were determined by HPLC assay and a modification of the method reported by Lee et al. [30]. Briefly, 50 μl of *n*-butyl *p*-hydroxybenzoate (2 μg/ml), as the internal standard, and 4 ml of *tert*-butylmethylether were added to 0.25 ml of the plasma samples. It was then mixed for 20 min using the rotamix and centrifuged at 5000 rev./min for 15 min. Three milliliters of the organic layer were transferred to a clean test tube and evaporated in a centrifugal evaporator at 30 °C. The residue was then dissolved in a 0.5 g/ml zinc sulfate solution [zinc sulfate/methanol/ethylene glycol (0.5 g:100 ml:1 ml)] and centrifuged at 5000 rev./min for 5 min, and a 50 μl of the solution was injected into the HPLC system.

The HPLC system consisted of a Waters 1515 isocratic HPLC Pump, a Waters 717 plus auto sampler, a Waters 2487 Dual λ absorbance detector (Waters Co., Milford, MA) and a computing integrator. The detector wavelength was set at 227 nm and the column was used at room temperature. The column used was a Symmetry $C_{18}$ column (4.6 × 150 $mm^2$, 5 μm, Waters Co., USA). Mixtures of acetonitrile/methanol/0.05 mM phosphate buffer (pH 4.0) (45:10:45, v/v/v) were used as the mobile phases at a flow rate of 1.2 ml/min. The retention times were as follows: internal standard, 5.3 min and paclitaxel, 7.7 min.

### 2.5. Pharmacokinetic analysis

The non-compartmental pharmacokinetic analysis was performed using the LAGRAN computer program [31], which uses the LAGRAN method to calculate the area under the curve (AUC) of the plasma concentration ($C_p$) as a function of time ($t$). AUC was computed using the LAGRAN method to reduce the errors associated with the trapezoidal rule. The mean residence time (MRT) was calculated as the area under the first moment curve divided by AUC. AUC was calculated using LAGRAN. The maximum plasma concentration ($C_{max}$) and the time to reach the maximum plasma concentration ($T_{max}$) were determined by a visual inspection of the experimental data. The elimination rate constant ($K_{el}$) was calculated by regression analysis from the slope of the line, and the half-life ($t_{1/2}$) of the drug was obtained by $0.693/K_{el}$. The absolute bioavailability (AB%) of paclitaxel after the oral administration compared to the i.v. administration was calculated as follows:

$$\text{Absolute bioavailability} = \frac{\text{Oral AUC}}{\text{i.v. AUC}} \times \frac{\text{i.v. dose}}{\text{Oral dose}} \times 100$$

The relative bioavailability (RB%) of paclitaxel after oral administration was calculated as follows:

$$\text{Relative bioavailability (AB)} = \frac{\text{AUC combined}}{\text{AUC control}} \times 100$$

### 2.6. Statistical analysis

All the means are presented with their SD (mean ± SD). An unpaired Student's *t*-test was used to determine any significant difference between the controls and prodrug pretreated with quercetin. The differences were considered to be significant at $P < 0.05$.

## 3. Results and discussion

The plasma profiles of paclitaxel after oral administration of the paclitaxel control (40 mg/kg) and the prodrug (280 mg, 40 mg as the paclitaxel) in animals pretreated with various doses of quercetin (2, 10, 20 mg/kg) are shown in Figs. 1 and 2. The bioavailability and the pharmacokinetic parameters of paclitaxel after the administration of paclitaxel or prodrug pretreated with quercetin are shown in Tables 1 and 2. When paclitaxel (40 mg/kg) or prodrug (280 mg/kg) were administered with quercetin (2, 10, 20 mg/kg), the plasma concentrations of paclitaxel were increased significantly ($P < 0.01$, for paclitaxel, $P < 0.05$, for prodrug) compared to the control. After the oral administration of paclitaxel pretreated with quercetin,

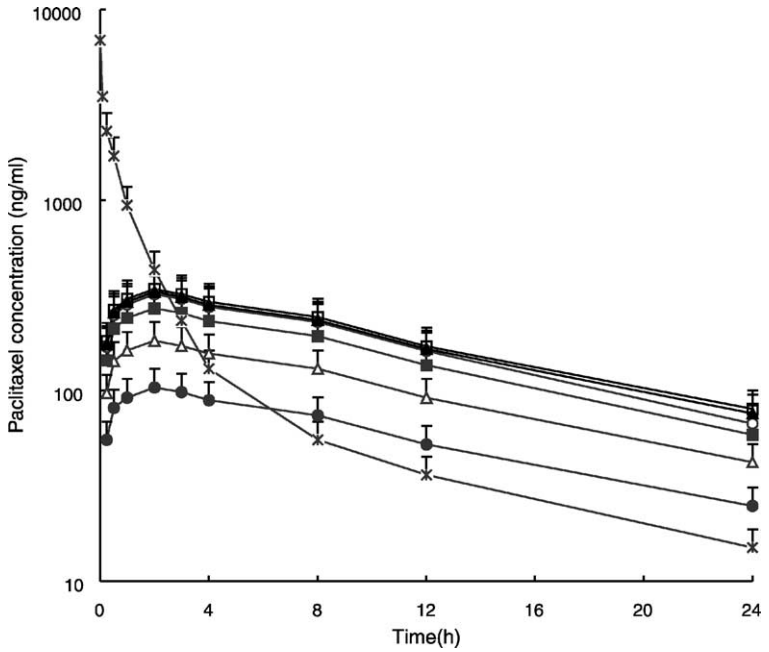


Fig. 1. Mean plasma concentration–time profiles of paclitaxel after oral administration of paclitaxel (40 mg/kg) to rats pretreated with quercetin(2, 10, 20 mg/kg). Bars represent the SD ($n = 8$). (●) paclitaxel control, (△) pretreated with quercetin 2 mg/kg, (■) pretreated with quercetin 10 mg/kg, (○) pretreated with quercetin 20 mg/kg. (▲) pretreated with quercetin 10 mg/kg for 3 days, (□) pretreated with quercetin 20 mg/kg for 3 days, ( ∗ ) i.v. 2 mg/kg.

the AUC and $C_{max}$ of paclitaxel pretreated with quercetin were increased significantly ($P < 0.01$) compared to the control. The $t_{1/2}$ and MRT were prolonged significantly ($P < 0.05$) compared to the control. The AB% of the paclitaxel control was 2.0, which was increased significantly ($P < 0.01$) by the pretreatment with quercetin (range between 3.5 and 6.6%). The RB% of paclitaxel with quercetin was 1.76- to 3.29-fold higher. On the other hand, the quercetin affected slightly the paclitaxel bioavailability, when paclitaxel-combined quercetin suspension was co-administered orally to rats [27–29]. For example, AUC and $C_{max}$ of cyclosporine co-administered with quercetin was decreased significantly compared to the control [29]. Paclitaxel was reported to be metabolized by cytochrome

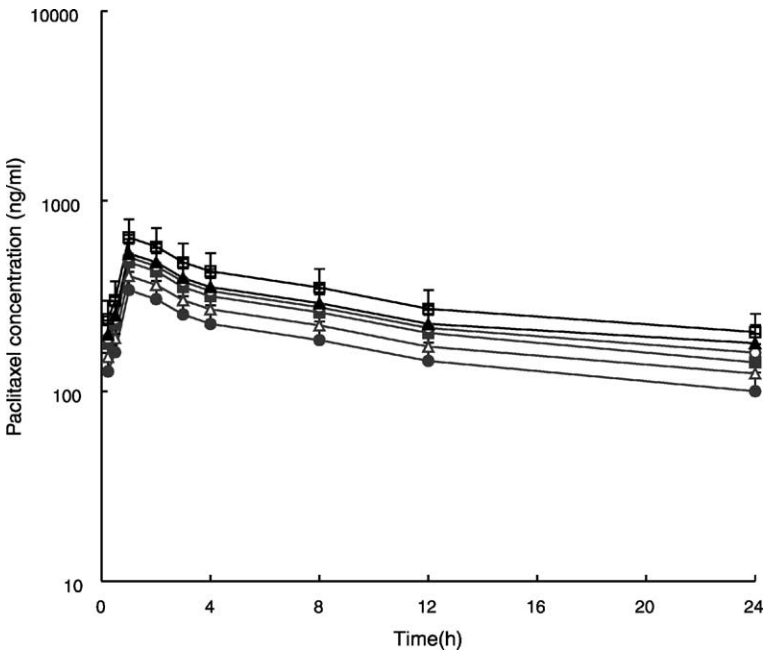


Fig. 2. Mean plasma concentration–time profiles of paclitaxel after oral administration of prodrug (280 mg/kg) to rats pretreated with quercetin (2, 10, 20 mg/kg). Bars represent the SD ($n = 8$). (●) prodrug control, (△) prodrug pretreated with quercetin 2 mg/kg, (■) prodrug pretreated with quercetin 10 mg/kg, (○) prodrug pretreated with quercetin 20 mg/kg, (▲) pretreated with quercetin 10 mg/kg for 3 days, (□) pretreated with quercetin 20 mg/kg for 3 days.

Table 1
Mean (± SD) pharmacokinetic parameters of paclitaxel after the oral administration of paclitaxel (40 mg/kg) to rats pretreated with quercetin

| Parameters | Paclitaxel control | Quercetin pretreat | | | | |
|---|---|---|---|---|---|---|
| | | 2 mg/kg | 10 mg/kg | 20 mg/kg | 3 days, 10 mg/kg | 3 days, 20 mg/kg |
| AUC (ng/ml h) | 1605 ± 409 | 2835 ± 721* | 4205 ± 1103** | 4978 ± 1211** | 5123 ± 1263** | 5301 ± 1328** |
| $C_{max}$ (ng/ml) | 104 ± 27 | 161 ± 31* | 248 ± 63** | 279 ± 71** | 288 ± 74** | 299 ± 76** |
| $t_{max}$ (h) | 2.0 ± 0.6 | 1.6 ± 0.5 | 1.5 ± 0.4 | 1.5 ± 0.5 | 1.5 ± 0.4 | 1.5 ± 0.4 |
| $t_{1/2}$ (h) | 9.9 ± 2.5 | 13.9 ± 3.5 | 16.6 ± 4.4* | 17.5 + 4.5* | 17.6 ± 4.6* | 17.9 + 4.7* |
| MRT (h) | 15 ± 3.8 | 22 ± 5.6 | 25 ± 6.4* | 26 ± 6.5* | 26 ± 6.4* | 26 ± 6.5* |
| AB% | 2.0 | 3.5* | 5.3** | 6.2** | 6.4** | 6.6** |
| RB% | 100 | 176 | 261 | 309 | 318 | 329 |

Mean ± SD ($n = 8$); *$P < 0.05$, **$P < 0.01$, significant difference compared to control; i.v. dose, 2 mg/kg; AUC, 3992 ± 902; $t_{1/2}$, 8.4 ± 2.1; MRT, 7.3 ± 1.8; AB%, 100; AUC, area under the plasma concentration–time curve from 0 to 24 h; $C_{max}$, peak concentration; $T_{max}$, time to reach peak concentration; $t_{1/2}$, terminal half-life; MRT, mean residence time; RB%, AUC rate compared to $AUC_{control}$; AB%, absolute bioavailability.

P-450 (CYP3A) both in the liver and in the epithelial cells of the small intestine. In addition, the absorption of paclitaxel was inhibited by the P-gp efflux pump in the intestinal mucosa [9,14–17]. The increased pharmacokinetic parameters of the AUCs, and $C_{max}$ may result from the inhibition of efflux pump, P-gp, in the intestinal mucosa. This result was consistent with the result reported by Scambia et al. [21] in that quercetin has the ability to inhibit the P-gp pump efflux. This result was also consistent with the result reported by Bardelmeijer et al. [32] and Malingre et al. [33] in that GF120918 and cyclosporin has the ability to inhibit the P-gp pump efflux, respectively. The prolonged $t_{1/2}$ and MRT may result from the inhibition of cytochrome P-450 by quercetin, as reported by Kumar et al. [15], and Rahman et al. [16]. It might be considered that the bioavailability of paclitaxel in a group pretreated with quercetin was significantly enhanced due to both the inhibition of cytochrome P-450 and the P-gp efflux pump in the intestinal mucosa.

This study, introduced a water-soluble prodrug compound, 7-mPEG 5000-succinyloxymethyloxycarbonyl-paclitaxel, which was obtained by introducing a new self-immolating linker that is spontaneously decomposed into paclitaxel combining a water-soluble polymer [23–26]. After the oral administration of the paclitaxel prodrug (280 mg/kg, 40 mg as the paclitaxel) to rats pretreated with quercetin, the AUC of paclitaxel was significantly ($P < 0.05$) higher than that of the prodrug control. The $t_{1/2}$ and MRT were significantly longer ($P < 0.05$). The AB% of paclitaxel in the prodrug control was 8.0, and that pretreated with quercetin increased significantly ($P < 0.05$) to 10.1 and 16.2%. The RB% was increased approximately 125–202% compared to that of the prodrug control. These results suggested that the bioavailability of paclitaxel in the prodrug was also promoted by pretreatment with quercetin, as mentioned above due to its potent P-gp and cytochrome P-450 inhibition in the gastrointestinal mucosa.

The molecular weight of paclitaxel and the prodrug is approximately 700 and 5000, respectively, and the bioavailability of paclitaxel as a result of administration of the prodrug with or without quercetin were remarkably higher than the paclitaxel control, which was more than 4- and 6- to 8-fold higher with quercetin. It might have resulted from the physicochemical properties of the prodrug, which is a water

Table 2
Mean (± SD) pharmacokinetic parameters of paclitaxel after oral administration of the paclitaxel prodrug (280 mg/kg, 40 mg as the paclitaxel) to rats pretreated with quercetin

| Parameters | Prodrug control | Quercetin pretreat | | | | |
|---|---|---|---|---|---|---|
| | | 2 mg/kg | 10 mg/kg | 20 mg/kg | 3 days, 10 mg/kg | 3 days, 20 mg/kg |
| AUC (ng/ml h) | 6384 ± 1719 | 8039 ± 2041 | 9458 ± 2542* | 10 066 ± 2546* | 10 539 ± 2562* | 12 901 ± 3348** |
| $C_{max}$ (ng/ml) | 339 ± 85 | 399 ± 106 | 452 ± 121 | 399 ± 106 | 516 ± 128* | 615 ± 189** |
| $t_{max}$ (h) | 1.5 ± 0.38 | 1.3 ± 0.29 | 1.3 ± 0.31 | 1.3 ± 0.29 | 1.3 ± 0.28 | 1.3 ± 0.28 |
| $t_{1/2}$ (h) | 15.5 ± 4.2 | 18.3 ± 5.0 | 18.0 ± 4.9 | 19.13 ± 5.0 | 22.0 ± 5.1* | 23.8 ± 5.5* |
| MRT (h) | 23 ± 6.0 | 24 ± 5.9 | 24 ± 5.6 | 25 ± 5.9 | 25 ± 6.3 | 26 ± 6.4* |
| AB% | 8.0 | 10.1 | 11.8* | 12.6* | 13.2* | 16.2** |
| RB% | 100 | 125 | 148 | 157 | 165 | 202 |

Mean ± SD ($n = 8$); *$P < 0.05$, **$P < 0.001$, significant difference compared to control; AUC, area under the plasma concentration–time curve from 0 to 24 h; $C_{max}$, peak concentration; $T_{max}$, time to reach peak concentration; $t_{1/2}$, terminal half-life; MRT, mean residence time; RB%, AUC rate compared to $AUC_{control}$; AB%, absolute bioavailability.

soluble compound and passes through the gastrointestinal mucosa more easily than paclitaxel without obstruction of P-gp and cytochrome P-450 in the gastrointestinal mucosa and it can be rapidly hydrolyzed by an esterase to generate the physiologically active paclitaxel [22], and leads to a high concentration of paclitaxel in the plasma resulting in higher bioavailability than the parent drug.

The AB% of the prodrug control was 8.0%, which is enough to be administered orally as a single dose. Based on these results, it might be feasible to develop an oral paclitaxel preparation, which is more convenient than the i.v. dosage forms.

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