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Self-micelle formation and the incorporation of lipid in the formulation affect the intestinal absorption of Panax notoginseng

Jing Xiong[a], Jianxin Guo[b], Luosheng Huang[c], Boyu Meng[a], Qineng Ping[a,*]

[a] Department of Pharmaceutics, China Pharmaceutical University, Nanjing 210009, PR China
[b] Technology Department, Talecris Biotherapeutics, 8368 US Hwy 70 West, Clayton, NC 27527, USA
[c] Department of Traditional Chinese Medicine, China Pharmaceutical University, Nanjing 210038, PR China

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ABSTRACT

The purpose of this research is to evaluate the effect of self-micelle formation and incorporation of lipid in the formulation on absorption of ginsenosides Rg1 and Rb1 from intestinal tract in rats. Ginsenosides Rg1 and Rb1 were extracted from Panax notoginseng saponins (PNS). The critical micellar concentration (CMC) of PNS in deionzied water was determined to be 0.339 mg/ml. At normal physiological ionic strengths, PNS was salted out from the solution above the CMC. The particle size of the micelle grows as PNS concentration increases. By in situ injection to a closed loop of the rat jejunum, $AUC_{0-6\,h}$ obtained after administration of low concentration solution (12 mg/ml) was 3.61 times for ginsenoside Rg1 and 3.84-folds for ginsenoside Rb1 compared with high concentration solution (120 mg/ml). The release rate of ginsenosides in aqueous medium was too slow to complete in 24 h, especially for Rb1. The data suggested that the self-micelle formation tendency in ginsenosides might prevent them from permeation or absorption through the cell membrane of gastrointestinal (GI) tract. To inhibit the formation of micelles, lipid was incorporated in the PNS formulation. The intraduodenal bioavailability in rats showed that the bioavailability was enhanced remarkably relative to the aqueous solution. $AUC_{0-\infty}$ of ginsenoside Rg1 and Rb1 in the lipid-based formulation were 207.52 ± 53.95 and 1961.72 ± 686.60 $\mu g\,ml^{-1}$ h, compared with 7.87 ± 2.85 and 148.58 ± 36.73 $\mu g\,ml^{-1}$ h, respectively from its aqueous solution. These findings suggested a new strategy to increase the absorption of amphiphilic saponins.

1. Introduction

Panax notoginseng is used as a therapeutic agent in Chinese traditional medicine. Pharmacological effects of Panax notoginseng have been described in the literatures (Cicero et al., 2003; Huang et al., 1999). Ginsenosides saponins extracted from Panax notoginseng (PNS) have been regarded as the principal components manifesting the pharmacological activities. Ginsenosides can be structurally classified into two groups, namely, the protopanaxadiol ginsenosides and protopanaxtriol ginsenosides (Fig. 1).

Ginsenoside Rg1 is one of the major triol saponins. It can excite central nervous system and has anti-fatigue and hemolysis properties. Ginsenoside Rb1 belongs to diol saponins and shows anti-inflammatory action, vasodilator effect and tranquilizing function (Takino, 1994; Benishin et al., 1991).

The PNS is poorly absorbed when administrated orally. Odani et al. (1983) reported that the amount of ginsenoside Rg1 absorbed via oral administration was within 1.9–20.0% of the dose. It was also reported that little ginsenoside Rb1 was absorbed from the digestive tract by orally administration to rats (Takino et al., 1982). The low bioavailability of PNS could be resulted from the decomposition in the stomach (Karikura et al., 1991; Takino, 1994) metabolism in the intestine (Akao et al., 1998; Bae et al., 2000; Hasegawa et al., 1997), and elimination in the liver. The bioavailability of ginsenoside Rg1 and Rb1 after portal venous administration are 50.56% and 59.49% (Han et al., 2005; Han and Fang, 2006).

Low membrane permeability is one reason for the poor absorption. Permeability is proportionally related to molecular size (molecular weight) or partitioning into lipid cell membrane. PNS are highly water-soluble substances. The molecular weights of ginsenoside Rg1 and Rb1 are larger than 500 (800 and 1108 Da, respectively). And there are more than 5 H-bond donors in their structures. According to the "rule of 5" (Swenson and Curatolo, 1992), these characteristics limit the absorption of PNS.

There is another reason that makes the permeability of ginsenosides Rg1 and Rb1 much worse. From the structure as shown in

* Corresponding author at: College of Pharmacy, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing, 210009, PR China. Tel.: +86 25 83271098; fax: +86 25 83301606.
E-mail address: pingqn@cpu.edu.cn (Q. Ping).

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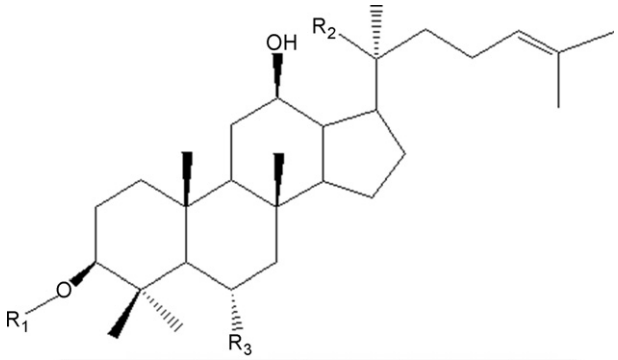

Compounds	R1	R2	R3	MW
Rg1	H	Glc	-O-Glc	800
Rb1	Glc2-Glc	Glc6-Glc	H	1108

Fig. 1. The structure of ginsenoside Rg1 and Rb1 of PNS (Glc: glucose).

Fig. 1, glucosyl group and triterpenoid dammarane group can be regarded as the hydrophilic and hydrophobic parts, respectively. It is possible that the molecules with such a structure would show the surface activity and might self-assemble as micelles in solution. If this is the case, the micellar aggregates might increase the molecular size and hydrophilic property. The result is very poor permeability either in paracellular or transcellular pathway.

In order to demonstrate our hypothesis, the critical micellar concentration (CMC) and particle size of PNS aqueous solution were determined. The effect of concentration on the intestinal absorption was elucidated by in situ closed loop assay. Release behavior of ginsenoside Rg1 and Rb1 from PNS aqueous solution was assessed. The effect of ionic strength on the solubility of PNS in aqueous solution was investigated as well.

Based on the understanding of self-micelle formation tendency, a lipid-based formulation was prepared by dissolving the PNS–phospholipids complex in the medium chain fatty glycerides. This new formulation was expected to prevent ginsenosides from aggregation and increase its absorption. The relative bioavailability of ginsenoside Rg1 and Rb1 from such a formulation was compared with the PNS aqueous solution by administration to rats.

2. Materials and methods

2.1. Materials

PNS was purchased from Kunming Phytopharmaceutical Co. Ltd. (Yunnan, PR China), phytochemically extracted from the roots of Panax notoginsneg. The percent contents of Rb1 and Rg1 in PNS were 36.95% and 30.45%, respectively. Phospholipid was purchased from Tai-wei-yao-ye Ltd., the phosphatidyl content was approximately 82% (w/w). Capmul MCM (C_8/C_{10} mono-/di-glycerides) were supplied by Karlshamns Lipid Specialties (Columbus, OH). Methanol (Sandong Yuwang Industrial & Commercial Co., Ltd.) was of HPLC grade. All the other chemicals were of reagent grade. Dialysis bags (molecular weight cut-off 10,000) were purchased from cole-parmer.

Sprague–Dawley rats weighting about 220–250 g were obtained from the Jiangsu animal breeding center, Nanjing. The animal studies were approved by the Animal Ethics Committee of China Pharmaceutical University. The rats were fasted for 20 h prior to the experiment.

2.2. Characterization of micelle solution

2.2.1. Determination of surface tension in the PNS aqueous solutions

A series of working solutions were prepared by dissolving PNS in water and physiologic saline respectively. The surface tension of working solutions was measured by tensiometer (DCAT 2.1, Dataphysics, Germany) at ambient.

2.2.2. Particle size

PNS aqueous solutions were prepared in deionzied water at different concentrations and filtrated through 0.8 μm filter. The particle size of the PNS solution was measured by dynamic light scattering (Zetasizer 3000 HSA, Malvern, UK).

2.2.3. The effect of ionic strength on the solubility of PNS

The effect of ionic strength on the solubility of PNS was investigated. Sodium chloride was employed to adjust the ionic strength from 0 to 0.2. The ionic strength in gastric and intestinal fluids falls within this range.

2.2.4. Release behavior of ginsenoside Rg1 and Rb1 from PNS micelle solution

The release of ginsenoside Rg1 and Rb1 from PNS micelle solution was conducted in 5% glucose solution at 37 °C in dialysis bags. Briefly, the PNS was dissolved in 1 ml 5% glucose solution and dialyzed against 100 ml glucose solution. Aliquots (2 ml) were removed at 0.35, 0.5, 1, 2, 4, 8, 12 and 24 h, respectively. Fresh medium (2 ml) was added after each sampling. The aliquots and the remaining sample in the dialysis bags at 24 h were filtrated through a 0.8 μm millipore membrane and determined for ginsenoside Rg1 and Rb1 amount by HPLC as described in 2.6. Each batch was analyzed in triplicate.

2.2.5. In situ closed loop assay

Intestinal absorption of PNS was examined in the in situ closed loop of the jejunum (Kamio et al., 2005). A midline abdominal incision was made, and the lumen of the jejunum was washed with saline. A jejunal loop (5 cm in length) was prepared by closing both ends with sutures. Different concentration of PNS aqueous solutions were prepared and then administered into the jejunal loop at a dose of 300 mg/kg. Blood samples were collected at the predetermined intervals. The plasma concentration of ginsenoside Rg1 and Rb1 was measured. The area under the plasma concentration-time curve from 0 to 6 h ($AUC_{0-6\,h}$) was calculated by the trapezoidal method from time zero to the final sampling time, 6 h.

2.3. Preparation of lipid-based formulation

2.3.1. Preparation of PNS–phospholipid complexes

PNS–phospholipid complex was prepared as previously reported (Xiong et al., 2008). Briefly, phospholipids and PNS at a quantity ratio of 1.2 (w/w) were dissolved in anhydrous tetrahydrofuran and stired for 2 h at 55 °C. After tetrahydrofuran was evaporated under vacuum at 40 °C, PNS–phospholipid complexes were collected and dried under vacuum at room temperature for 24 h.

2.3.2. Preparation of lipid-based formulation

Lipid–based formulation were prepared by dissolving PNS phospholipids complex in Capmul MCM at 60 °C to produce a homogeneous and clear oil formulation at the concentration of 90.9 mg PNS in 1.0 g of lipid.

2.3.3. Determination of ginsenoside Rg1 and Rb1 in lipid-based formulation

Lipid-based formulation (50 mg) was dissolved in 10 ml of methanol and a 20 μl aliquot was injected into HPLC as described in Section 2.6.

2.4. Dissolution of ginsenosde Rg1 and Rb1 from PNS lipid-based preparation

Accurately weighed PNS lipid-based preparation (500 mg) was dispersed in water and incubated at 37 °C with continuous shaking (200 rpm) to monitor the dissolution of ginsenoside Rg1 and Rb1. The weight ratio of aqueous phase and the formulation was 1:10. At predetermined time intervals the aqueous phase was taken and the concentrations of ginsenoside Rg1 and Rb1 were analyzed by HPLC.

2.5. Pharmacokinetic study of PNS aqueous solution and lipid-based preparation in rats

PNS aqueous solution (120 mg/ml) and lipid-based preparation (90.9 mg/ml) were administered intraduodenally at a dose of 600 mg/kg to fasted rats with free access to water. Each group contains six rats. Blood samples were collected at 5, 20, 40, 60 min, 1.5, 2, 4, 8, 12, 24, 48, 72 h, respectively after intraduodenally administration under light ether anaesthesia and pretreated with solid phase extraction (SPE) cartridges (OASIS®, Waters, USA).

Ginsenoside Rg1 and Rb1 plasma levels in rats were assessed by HPLC as described in 2.6. The lower limits of concentration were 534 and 800 ng/ml for Rg1 and Rb1, respectively. The mean recoveries for Rg1 and Rb1 were 91.88 ± 5.27% and 92.06 ± 5.93%, respectively. The intra- and inter-day precision for Rg1 and Rb1, determined as relative standard deviations, were less than 5.0%. The calibration equation for Rg1 was $M = 13.179A + 20.522$ ($r = 0.9991$). And the equation for Rb1 was: $M = 16.42A + 47.591$ ($r = 0.9993$). M is drug mass and A is peak area. The method has been demonstrated to be sensitive and accurate for the determination of Rg1 and Rb1 in rat plasma.

2.6. HPLC assay of ginsenoside Rg1 and Rb1

The concentration of ginsenoside Rg1 and Rb1 was determined by HPLC. The HPLC system was consisted of two pumps (HP1100, Agilent, USA), a Diamonsil C_{18} column (4.6 i.d. × 250 mm, 5 μm, Dikma, Beijing, China) maintained at 35 °C, an UV detector (HP1100, Agilent, USA) set at 203 nm and an autosampler (HP1100, Agilent, USA). The HP1100 ChemStation software was applied on the HPLC system.

Gradient elution was performed using water (A) and acetonitrile–water (65:35, v/v) (B). Initial condition was A–B (62:38, v/v), linearly changed to A–B (36:64, v/v) at 32.5 min. The post-time was 6 min. And the flow rate was 1 ml/min.

2.7. Surface tension data analysis

The relationship between the surface tension and the concentration of PNS solution has been statistically analyzed by SPSS 13.0 software. Fitting was made by the cubic equation. Cubic regression equation can be expressed as:

$$\mathrm{SFT} = A \times \mathrm{CON}^3 + B \times \mathrm{CON}^2 + C \times \mathrm{CON} + D$$

where A, B and C are the regression coefficients and D the regression constant. The SFT (surface tension of solution) is a dependent variable while CON (concentration of PNS) is an independent variable. We can take the first derivative of the cubic equation. The CMC can be calculated by setting the derivative SFT as zero, according to its definition.

2.8. Pharmacokinetic data analysis

The AUC for ginsenoside Rg1 and Rb1 after administration was obtained using the linear trapezoidal rule from time zero to the last measured time point, followed by the addition of the extrapolated tail area. The tail area can be calculated by dividing the last measured plasma concentration by the terminal rate constant.

The results are expressed as the mean ± S.D. and statistical analysis was performed using Student's unpaired t-test. A value of $P < 0.05$ was considered to be significant difference for all tests used.

3. Results and discussions

3.1. Characterization of PNS micelle solution

3.1.1. CMC estimation

The presence of an amphiphilic molecule in aqueous solution decreases the surface tension significantly as the surfactant concentration increases till the micelles form. The average surface tensions of PNS aqueous solutions were analyzed and the coefficients of the cubic model were estimated by regression analysis. The regression profile is shown in Fig. 2. A good correlation exists between the surface tension and the concentration of PNS aqueous solution. The CMC of PNS aqueous solution was determined to be 0.339 mg/ml, based on first derivative of the cubic equation when setting $d\mathrm{SFT}/d\mathrm{CON} = 0$. PNS was administered to rats at a concentration of 120 mg/ml, a common employed concentration in the studies of oral bioavailability, which is far beyond the CMC. So, ginsenoside Rg1 and Rb1 molecules exit as micelles. The hydrophobic portions of ginsenoside Rg1 and Rb1 are oriented within the cluster and the hydrophilic portions are exposed to the solvent, which results in high hydrophilic property.

3.1.2. Particle size

A micelle may take several forms, depending on the composition of its components and the solution conditions such as concentration, temperature, pH, and ionic strength. Fig. 3 shows the linear relationship between particle size and the concentration of PNS. The particle size grows from 11.06 to 40 nm as the concentration increases from 120 mg/ml to 600 mg/ml at ambient. As ginsenoside Rg1 and Rb1 are absorbed via passive diffusion along a concentration gradient (Han et al., 2005; Han and Fang 2006) the size of particles has a great impact. As the average intercellular space for passive diffusion (paracellular pathway) is less than 8.43 ± 1.43 Å

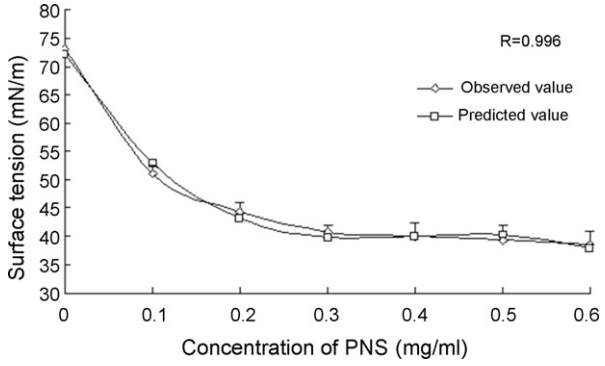

Fig. 2. Surface tension as a function of concentration in PNS aqueous solution. Each point represents the mean ± S.D. for three independent samples.

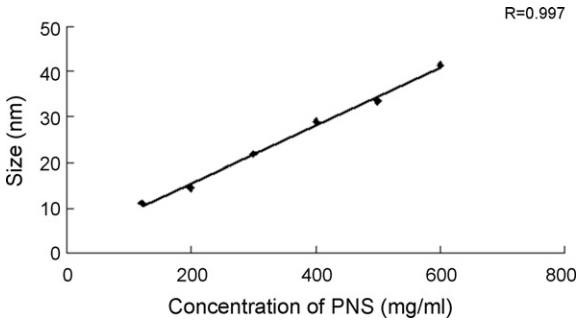

Fig. 3. Relationship between the concentrations of PNS aqueous solution and its particle size.

(Adson et al., 1994), the large size (11.06 nm for 120 mg/ml) makes ginsenosides difficult to be absorbed either by paracellular pathway or by transcellular pathway.

3.1.3. Effect of ionic strength on the solubility of PNS in aqueous solution

In present study, ions were found to have an impact on CMC value of PNS aqueous solution. According to the analysis procedure as described in Section 2.6, the CMC decreased from 0.339 mg/ml in deionized water to 0.282 mg/ml in physiologic saline. In general, the addition of ions affects the hydration of the surfactant in aqueous solution. As the concentration of ions increases, more water is required to keep the ions soluble. The amount of water available to hydrate the surfactant is reduced, so the solubility of the surfactant decreases.

We have investigated how the ionic changes affected the solubility of PNS. When the concentration was 300 μg/ml (above the CMC), the saline solution became cloudy after 30 min. The solution remained clear even after 24 h when PNS concentration was only 200 μg/ml (below the CMC). On the other hand, as NaCl concentration in the solution increases, the solubility of PNS decreases accordingly. PNS solution (200 μg/ml) became cloudy when the ionic strength was greater than 0.2. These results indicated that the solubility was influenced by ionic strength.

Under the applied dose (120 mg/ml), PNS was salted out from its aqueous solution when the ion strength reached 0.01. Therefore, PNS is likely to be salted out in vivo within the normal ranges of gastric and intestinal ionic strengths (0.01–0.2) (Johnson et al., 1993). We have observed the precipitation of PNS in physiologic saline by a microscopy.

3.1.4. Release behavior of ginsenoside Rg1 and Rb1 from PNS micelle solution

Figs. 4 and 5 showed release profiles of ginsenoside Rg1 and Rb1 from PNS solutions at different concentrations. It appears that the release rate from 1 mg/ml solution was remarkably greater than from higher concentrations.

As to ginsenoside Rg1, 85.55% Rg1 was released from 1 mg/ml PNS solution within 4 h while less than 35% Rg1 was released from 100 mg/ml PNS solution within 24 h. Rg1 can be released completely within 24 h when the concentration of PNS was below or equal to 50 mg/ml.

The release of ginsenoside Rb1 from PNS solution displays similar tendency with lower rate. Only 9.92% Rb1 released from 10 mg/ml PNS solution within 8 h. In contrast, the accumulated release of Rg1 was about 85%. Furthermore, less than 10% Rb1 was released from 50 to 100 mg/ml PNS solution within 24 h.

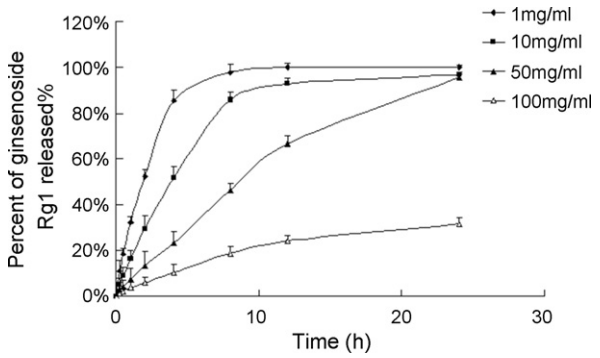

Fig. 4. The release rate profile of ginsenoside Rg1 from PNS solution at different concentrations. PNS solutions were prepared in 5% glucose solution. Each point represents the mean ± S.D. for three independent samples.

The low release rate and incomplete release of ginsenosides resulted in low concentration of free molecules which might limit the permeation or absorption of ginsenosides through the cell membrane of gastrointestinal (GI) tract.

3.1.5. In situ closed loop study

The particle size grows as the concentration of PNS increases. The effect of concentration on the intestinal absorption was elucidated by in situ injection to a closed loop of the rat jejunum. As shown in Table 1, $AUC_{0-6\,h}$ obtained after administration of low concentration solution (12 mg/ml) was 3.61 times for ginsenoside Rg1 and 3.84-folds for ginsenoside Rb1 compared with high concentration solution (120 mg/ml).

3.2. Dissolution of ginsenoside Rg1 and Rb1 from PNS lipid-based preparation

The release profiles of ginsenoside Rg1 and Rb1 from lipid-based preparation were shown in Fig. 6. Ginsenoside Rg1 and Rb1

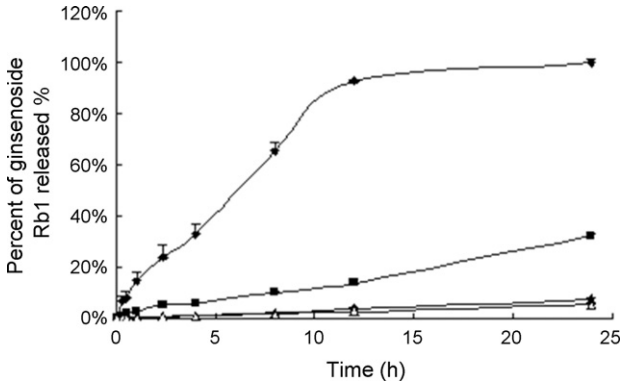

Fig. 5. The release rate profile of ginsenoside Rb1 from PNS solution at different concentrations. PNS solutions were prepared in 5% glucose solution. Each point represents the mean ± S.D. for three independent samples.

Table 1
Comparison of intestinal absorption of PNS solution at different concentrations

Concentration of PNS (mg/ml)	$AUC_{0-6\,h}$ (μg^{-1} ml h)		Enhance factor	
	Rg1	Rb1	Rg1	Rb1
120	9.46 ± 1.41	38.88 ± 6.75	1	1
12	34.13 ± 9.02	149.36 ± 28.36	3.61**	3.84**

Each value represents the mean ± S.D. of four animals.
Symbols represent significant values between groups (** $P < 0.01$)

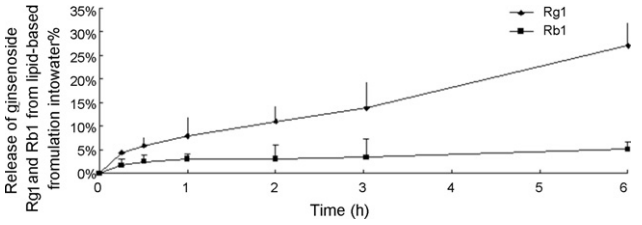

Fig. 6. In vitro release of ginsenoside Rg1 and Rb1 in PNS complex oil solution into aqueous phase. Each point represents the mean ± S.D. for three independent samples.

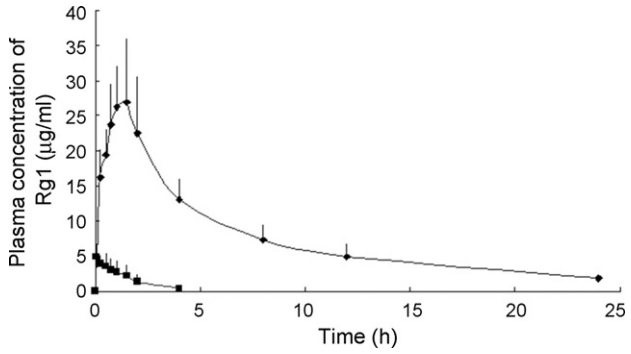

Fig. 7. Plasma concentration–time profiles of ginsenosides Rg1 after intraduodenally administration of PNS (600 mg/kg) to rats. Each point represents the mean ± S.D. of six animals. Aqueous solution (■); lipid-based formulation (□).

were released from the formulation slowly. Less than 30% Rg1 and approximately 5% Rb1 were released from the complex oil solution within 6 h.

The data suggested that the lipid-based formulation effectively slowed down the diffusion rate of the molecules to the aqueous phase and prevented the formation of the micelles.

3.3. Relative bioavailability in vivo by intraduodenally administration

Figs. 7 and 8 respectively showed that the mean plasma concentration profiles of ginsenoside Rg1 and Rb1 after administration of PNS aqueous solution and lipid-based formulation.

After given as PNS aqueous solution, Rg1 reached peak concentration (4.88 μg/ml) in plasma rapidly within 5 min and was practically undetectable 4 h later. While the maximum concentration (C_{max}) and time to maximum concentration (T_{max}) of Rg1 was 26.9 μg/ml and 1.5 h after administration of lipid-based formulation. And it could still be detected at 24 h after administration.

Similar to the result of ginsenoside Rg1, Rb1 was absorbed through the GI tract rapidly after administration as aqueous solution. It reached the maximum concentration (6.06 μg/ml) at 15 min. After administration of lipid-based formulation, Rb1 was extensively absorbed with bio-absorption peak. Rb1 concentration reached the minor initial maximum concentration of

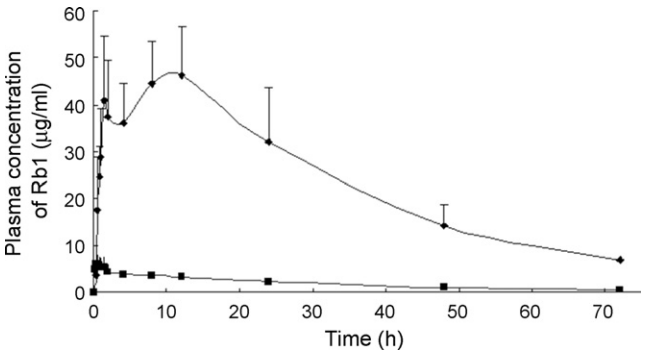

Fig. 8. Plasma concentration–time profiles of ginsenosides Rb1 after intraduodenally administration of PNS (600mg/kg) to rats. Each point represents the mean ± S.D. of six animals. Aqueous solution (■); lipid-based formulation (□).

40.88 μg/ml at 1.5 h and the major secondary peak of 46.20 μg/ml at 12 h.

As shown in Table 2, the $AUC_{0-\infty}$ of ginsenoside Rg1 after intraduodenal administration of PNS aqueous solution and lipid-based formulation were 7.87 ± 2.85 and 207.52 ± 53.95 μg/ml^{-1} h, respectively. A statistically significant difference was observed ($p < 0.01$). The intraduodenal bioavailability of ginsenoside Rg1 in lipid-based formulation was 28.38 fold greater than that obtained after administration of aqueous solution ($p < 0.05$) at the dose of 120 mg/kg.

The tendency is the same for ginsenoside Rb1. Ginsenoside Rb1 administered as lipid-based formulation shows significantly higher plasma levels relative to the aqueous solution. The $AUC_{0-\infty}$ values of ginsenoside Rb1 after intraduodenally administration of PNS aqueous solution and the lipid-based preparation were 148.58 ± 36.73 and 1961.72 ± 686.60 μg ml^{-1} h, respectively. The relative bioavailability of ginsenoside Rb1 in the formulation was 1320% ($p < 0.05$) in comparison with PNS aqueous solution.

The formation of micelles has two impacts. One is the increase in size and hydrophilicity, the other is the salting out of the substances in normal gastric and intestinal ionic strengths. Both aspects will limit the dissolution of PNS in vivo and lead to poor absorption. By application of lipid-based formulation, the existing state of the drugs *in vivo* is changed. The phospholipid complex in which a layer of phospholipid molecules wrapped around drug molecules (Roger and Christopher, 1997) has allowed drug molecules to be solubilized in bulk oil phase in the absence of water. When the complex is dissolved in oil, the hydrophilic portions of PNS are oriented within the cluster and the hydrophobic portions are exposed to the oil. Even when drug molecules diffuse to the gastrointestinal fluid, the hydrophilic micelles are less likely to form with the presence of phospholipid. Therefore, the absorption pathway may be altered.

In addition, middle chain fatty glyceride might enhance the ability particles to pass across the cell layer (Beskid et al., 1988; Constantinides et al., 1994; Unowsky et al., 1988; Yeh et al., 1995; Ueda et al., 1983). Furthermore, the ginsenosides prepared as lipid-based formulation might be absorbed in the similar way as lipids.

Table 2
$AUC_{0-\alpha}$ values of ginsenoside Rg1 and Rb1 following administration as the aqueous solution and the lipid-based formulation

Dosage form	$AUC_{0-\alpha}$ (μg^{-1} ml h)		Absorption-enhancing factor	
	Rg1	Rb1	Rg1	Rb1
Aqueous solution	7.87 ± 2.85	148.58 ± 36.73	1	1
Lipid-based formulation	207.52 ± 53.95	1961.72 ± 686.60	26.38**	13.20*

Each value represents the mean ± S.D. of six animals.
Symbols represent significant values compared with that of aqueous solution (* P < 0.05, ** P < 0.01)

Finally, the extension of the absorption time resulted from the slow movement of the oil in GI tract and the protection against the degradation of gastro-intestinal glucoside hydrolase by preventing these molecules from diffusing to aqueous phase might also improve the relative bioavailability. All these factors mentioned above could promote the absorption of PNS.

PNS is highly water-soluble but poor absorbed when administered orally. So, it is classified as Class III drug according to the Biopharmaceutics Classification System (Yamamura et al., 1995). The saponins that are mainly produced by plants, lower marine animals and some bacteria are naturally occurring surface- glycosides. They exhibit a sugar moiety from glucose, galactose, glucuronic acid, xylose, rhamnose or methylpentose. They are glycosidically linked to a hydrophobic aglycone (sapogenin) which may be triterpenoid or steroid in nature. For hydrophilic and amphiphilic saponins, absorption is less dependent on the drug dissolution properties while permeation through the intestinal membrane becomes the rate limiting process for oral absorption. Therefore, the lipid-based formulation combining phospholipids complex with lipophilic oil phase could be a useful method for improving the absorption of amphiphilic saponins.

4. Conclusions

The present study demonstrates that ginsenoside Rg1 and Rb1 can aggregate into micelles in PNS aqueous solution and salt out in GI tract fluid containing electrolytes. Such an aggregation limits the permeation of ginsenoside Rg1 and Rb1 through cell membrane of GI tract. In order to solve the problem, a new lipid-based formulation was designed to prevent PNS from forming the micelles. After intraduodenal administration of the new formulation, bioavailability in rats was enhanced remarkably relative to the aqueous solution. These findings reveal a new strategy to increase the absorption of the amphiphilic drugs especially for saponins.

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