International Journal of Pharmaceutics 360 (2008) 191–196

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

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

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ARTICLE INFO

Article history:
Received 20 November 2007
Received in revised form 20 March 2008
Accepted 11 April 2008
Available online 16 April 2008

Keywords:
Panax notoginseng
Ginsenoside Rg1
Ginsenoside Rb1
Self-micelle formation
Lipid-based formulation
Enhanced absorption

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.

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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

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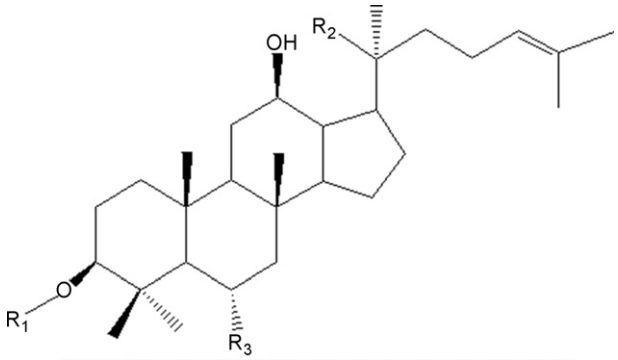
0378-5173/$ – see front matter © 2008 Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2008.04.016



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.

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