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Pharmacokinetics study of bio-adhesive tablet of *Panax notoginseng* saponins

Hanzhou Feng, Wei Chen and Chunyan Zhu*

Abstract

Panax notoginseng saponin (PNS) is the main active gradient of Chinese traditional medicine *Panax notoginseng*. Although its prominent therapeutic efficacy has been demonstrated by various researchers, the broader application is restricted by the low bioavailability of PNS. This article aims to discuss PNS's plasma pharmacokinetics after oral administration of bio-adhesive tablet of PNS to beagle dogs and improve its bioavailability in comparison with normal tablet. The bio-adhesive tablet was prepared according to our previous patent, using chitosan as main excipient. A simple and sensitive LC-MS/MS combined with solid-phase extraction (SPE) method for the analysis of PNS in dog's plasma was developed in our previous study, and was validated to apply in the pharmacokinetics study in this work. Three ingredients: Notoginsenoside R1 (R1), Ginsenoside Rg1 (Rg1) and Ginsenoside Rb1 (Rb1) (Figure 1), were chosen as indicators of PNS to analyze it in vivo. Statistically significant increase ($P < 0.05$) in pharmacokinetic parameters of PNS including AUC and Tmax for R1, Rg1 and Rb1, Cmax for R1 and Rb1, MRT for Rg1 were obtained after oral administration of bio-adhesive tablet of PNS comparing with its normal tablet. The formulation modification of using chitosan to prepare bio-adhesive tablet for oral administration is effective in improving the bioavailability of PNS, thereby enhancing its potential therapeutic effect and broadening its clinical application.

1. Introduction

Panax notoginseng (Burk.) F.H. Chen is an important traditional Chinese medicine mainly produced in Yunnan, Guangxi and Szechwan in China. *Panax notoginseng* saponin (PNS), the extract of *Panax notoginseng*, has been generally studied. PNS possesses many pharmacological active effects, including resistance against cerebral infarction and ischemia by inhibiting apoptosis and expression of caspase-1 and caspase-3 [1,2]; antioxidant property by its strong ferrous ion chelating activity scavenging activities against hydrogen peroxide, hydroxyl radicals, superoxide anion and DPPH free radicals [3]; therapeutic effect on atherosclerosis by lowering serum lipid level and regulating expression of vascular cell differentiation antigen 40 and matrix metalloproteinase 9 [4]. In recent years, increasing attention has been paid to other activities of PNS: neuroprotective activity based on its potent protective effect against blood-brain

barrier damage) [5]; anti-hyperglycemic and anti-obese effects by lowering fasting blood glucose levels and improving glucose tolerance [6]; anti-platelet and anti-coagulant effects [7]; anti-inflammatory in vitro properties via blocking NF- κ B signaling pathway in macrophages [8]; anti-depressive activity that may be mediated by modulation of brain monoamine neurotransmitters and intracellular Ca²⁺ concentration (Xiang et al.: The antidepressant effects and mechanism of action of total saponins from the caudexes and leaves of *Panax notoginseng* in animal models of depression, submitted).

Currently, there are some commercial formulations of PNS in China, including XUESAITONG tablet, injection and lyophilized powder injection. However, the oral bioavailability of PNS is not satisfying, and it is documentarily reported that some adverse reactions such as epistaxis, allergy and even anaphylactic shock might be caused by using PNS injection [9]. In order to avoid such serious adverse effects as well as to improve the oral bioavailability of PNS, developing more appropriate formulation is urgently needed. In our lab's previous studies, we applied a widely used bio-adhesive excipient, carbopol, to make bio-adhesive tablet [10]. However, chitosan is a more

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bio-compatible excipient, it has been reported that the median lethal dose (LD50) for mice after oral administration of chitosan is 16 g/kg. Thus the toxicity of chitosan is considerably lower than carbopol, the LD50 of which is 2.5 g/kg [11]. Based on the consideration of choosing an excipient with lower toxicity, in this study we used chitosan to prepare bio-adhesive tablet.

Researchers have done some pharmacokinetics studies of PNS [12,13], most of these studies chose Ginsenoside Rg1 or Ginsenoside Rb1 as indicator of PNS for analyzing. Although reported detection method simultaneously analyzed Notoginsenoside R1, Ginsenoside Rg1, Rd, Re and Rb1 in rat plasma by HPLC/ESI/MS [14], their sample preparation method using liquid-liquid extraction is different from our solid-phase extraction (SPE) method. In our study, we adopted a liquid chromatography-tandem mass spectrometry (LC/MS/MS) combined with SPE method established in our previous study to simultaneously detect Notoginsenoside R1, Ginsenoside Rg1 and Rb1 to reflect the veritable pharmacokinetics properties of PNS in plasma sample of beagle dogs [15]. The chemical structures of the three components are shown in Figure 1. It is expected that this research would be effective for improving bioavailability of PNS and their clinical therapeutic efficacy, and can serve as a significant foundation for further pharmacological studies of PNS.

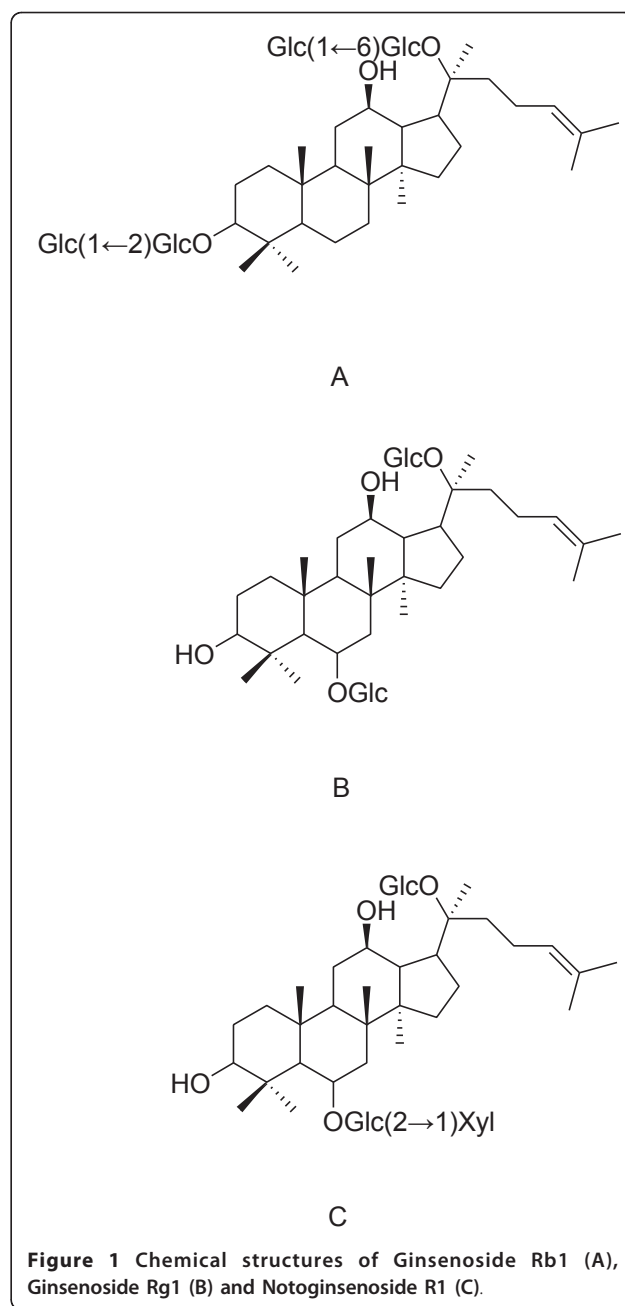
2. Experimental

2.1. Instruments

Blood samples were pretreated with extract-clean C18 (solid-phase extraction) cartridge columns (1 mL, packed with 100 mg of 40 μ m octadecyl silica) (Alltech Company, Deerfield, USA). The assay was performed on an Agilent 1100 series HPLC system (Agilent Technologies, Waldbronn, Germany) consisting of a quaternary pump, a triple quadrupole mass spectrometry detector, an autosampler, a vacuum Degasser and a column oven. The mass spectrometer (ABI, USA) equipped with a turboionspray source was used for the analysis. The mobile phase with the flow rate of 0.2 ml/min consisting of 10 mM ammonium acetate solution, 0.1% n-butyl-amine, 10% methanol in water (A) and methanol (B). The system was run by a gradient program of 50% B to 90% B in five minutes and 90% B to 50% B in three minutes. Single-punch tablet press (TDP, Tianxiang pharmaceutical machinery factory, Shanghai)

2.2. Materials

PNS extract was purchased from the Institute of Medicinal Plant Development, Yunnan Branch (Yunnan Province, China). PNS extract contained 37% of Rg1, 36% of Rb1, and 10% of R1, respectively, according to HPLC analysis. Standards of R1, Rg1 and Rb1 were purchased



from the National Institute of the Control of Pharmaceutical and Biological Products (Beijing, China). In addition, Glipizide (internal standard) was generously provided by Professor Jifen Guo at the Academy of Military Medical Sciences (Beijing, China). Chitosan was purchased from Jinqiao Biochemistry Company (Zhejiang, China). Acetonitrile and methanol (HPLC grade) were purchased from Fisher Scientific (New Jersey, USA). The heparin sodium was purchased from Beijing Yaobei Biological and Chemical Reagents Company (China).

2.3. Animals

Six male beagle dogs, weighing at 10-12 kg, from Tongli Laboratory Animals Center (Beijing, China) were adopted in the animal experiments. The Experiments were carried out in accordance with international accepted guidelines on laboratory animal use, the Guide for the care and use of laboratory animals (Institute of Laboratory Animal, Washington, D.C. National Academy Press 1996), and the protocols were approved by the Beijing Animal Care Committee (Beijing, China).

2.4. Preparation of blood samples

Solid phase extraction (SPE) cartridges were preconditioned by passing through 2 ml of methanol followed by 2 ml of water before loading. 0.5 ml plasma sample was applied to solid phase extraction cartridge (1 ml, packed with 100 mg of 40 μ m octadecyl silica) and drawn through by gravity. The cartridge was washed chronologically with 2 ml of water, 2 ml of 20% (v/v) aqueous methanol solution, and 2 ml of methanol. The final methanol eluate was collected and 10 μ L of internal standard was added to it. The eluate was thereafter evaporated at 60°C to dryness under a stream of nitrogen. The residue was dissolved in 100 μ L of 50% (v/v) aqueous methanol solution. A 20 μ L sample was injected into the HPLC system for analysis.

2.5. Preparation of normal and bio-adhesive tablet of PNS

We prepared normal tablet and bio-adhesive tablet according to our previous patent (Patent number: ZL200510073274.4). The ratio between PNS and other excipients in our two kinds of tablets was PNS: chitosan: other excipients = 60:40:100. Based on the standard of commercial XUESAITONG tablet, the dosage of PNS in our both bio-adhesive and normal tablet was 50 mg. We homogeneously mixed PNS with other excipients except chitosan after sifting, and used ethanol to wet-granulate particles. The particles passed through 20-mesh sieve were dried at 60°C. Then they were mixed with chitosan and magnesium stearate and were compressed into tablets by using a single-punch tablet press. Normal tablet was prepared by the similar ratio and method, without adding chitosan.

2.6. Administration of PNS and sample collection

According to our double cycle and crossover experimental design, normal and bio-adhesive tablets were administered orally at a dose of 90 mg/kg to six beagle dogs. All dogs were deprived of food but given free access to water for 12h before the experiments. Blood samples (3 ml each time) were collected via fore leg vein of dogs according to the specific time intervals of at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72h after administration. The plasma was separated after centrifugation for

10 mins at 3000 r·min⁻¹ and stored at -20°C for the further analysis.

2.7. In vivo pharmacokinetic study

All the data was processed by non-compartmental analysis using the Phoenix WinNonlin 6.1 (Pharsight, USA), and then was analyzed by SPSS software to judge its significance.

3. Results and Discussion

3.1. Validation of LC-MS/MS methods

The specificity was evaluated by comparing chromatograms of blank plasma (from six different dogs), blank plasma spiked with R1, Rg1, Rb1, internal standard, and plasma samples after oral administration of by bio-adhesive tablet of PNS. As they were shown in Figure 2, 3, and 4, these chromatographic conditions revealed that there was no significant interfering endogenous peak observed within the period where R1, Rg1, Rb1 and internal standard were detected. Linearity of the calibration curves was found over the range of 2.8-140 ng for R1, 3.8-190 ng for Rg1 and 18-900 ng for Rb1. The equation of calibration curve for R1 was $y = 0.0024x + 0.0068$ ($r^2 = 0.9967$), for Rg1 was $y = 0.001x + 0.0015$ ($r^2 = 0.9991$); for Rb1 was $y = 0.001x + 0.0197$ ($r^2 = 0.9982$). The accuracy and precision were evaluated by quality control samples at low (2.8 ng/ml for R1, 3.8 ng/ml for Rg1 and 18 ng/ml for Rb1), medium (14 ng/ml for R1, 19 ng/ml for Rg1 and 180 ng/ml for Rb1), and high (140 ng/ml for R1, 190 ng/ml for Rg1 and 900 ng/ml for Rb1) concentrations which were prepared in the same way as calibration standards. The intra-batch accuracy and precision of the assay were assessed by quality control samples analysis at three concentrations in six replicates and the inter-batch was detected by analyzing them in three batches. The results met our requirement for detecting, and the detailed data have been published in our previous research article [15]. The relative recovery for R1 was 96.02% at 2.8 ng/ml, 104.02% at 14 ng/ml and 102.32% at 140 ng/ml; for Rg1 was 99.92% at 3.9 ng/ml, 102.40% at 19 ng/ml and 98.96% at 190 ng/ml; for Rb1 was 102.67% at 18 ng/ml, 101.13% at 180 ng/ml and 105.00% at 900 ng/ml, the standard deviations were lower than 10.2%. The validated method was proved to be sensitive, reliable and the data demonstrated that this method was successfully applied to study the pharmacokinetics of PNS in beagle dogs after oral administration of PNS tablets.

3.2. Pharmacokinetic applications and plasma drug concentration-time curves of six beagle dogs

The highly developed digestive system of beagle dog is more similar to human and is more appropriate for pharmacokinetics study of medicine, especially for medicine passing through gastrointestinal tract [16]. In this

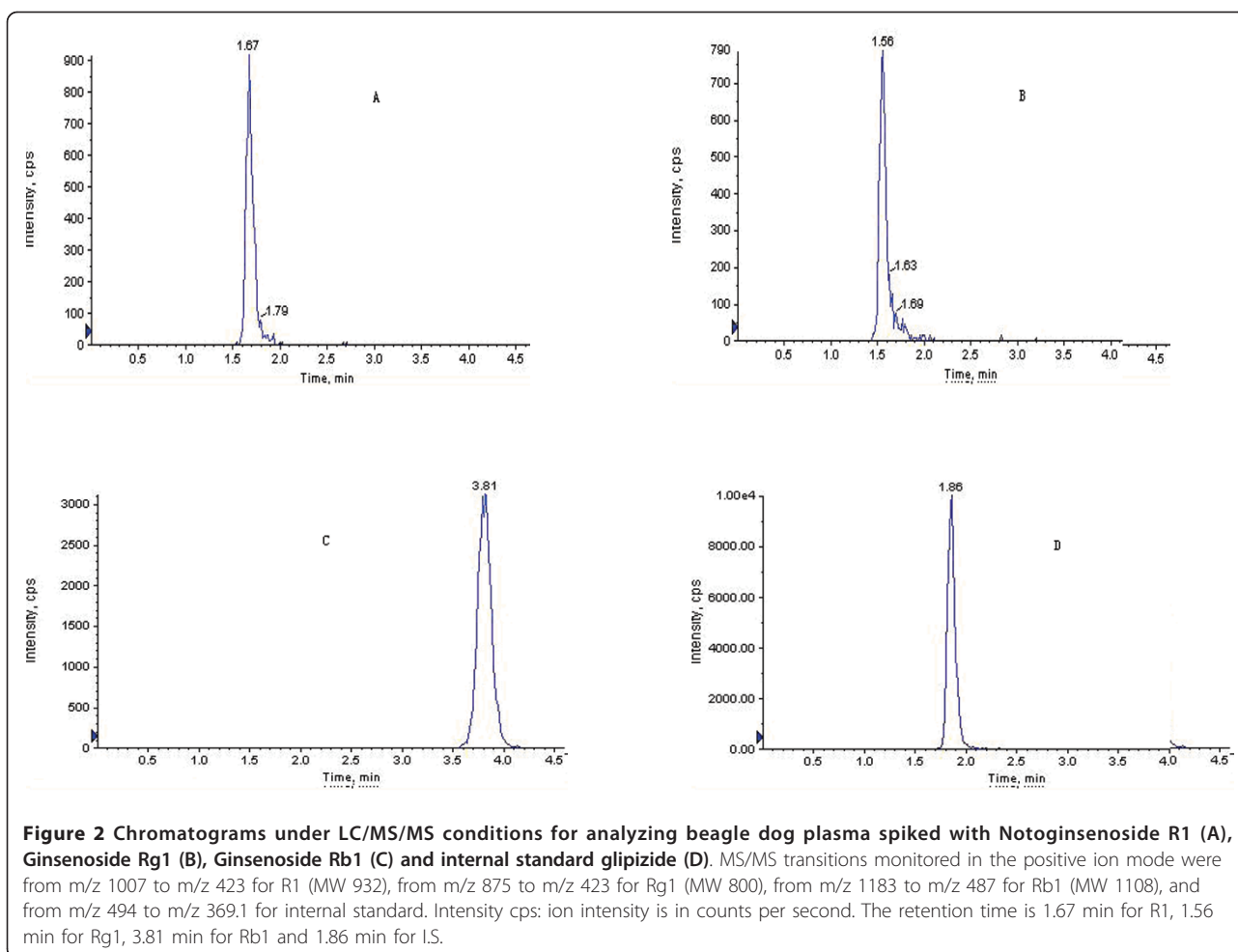


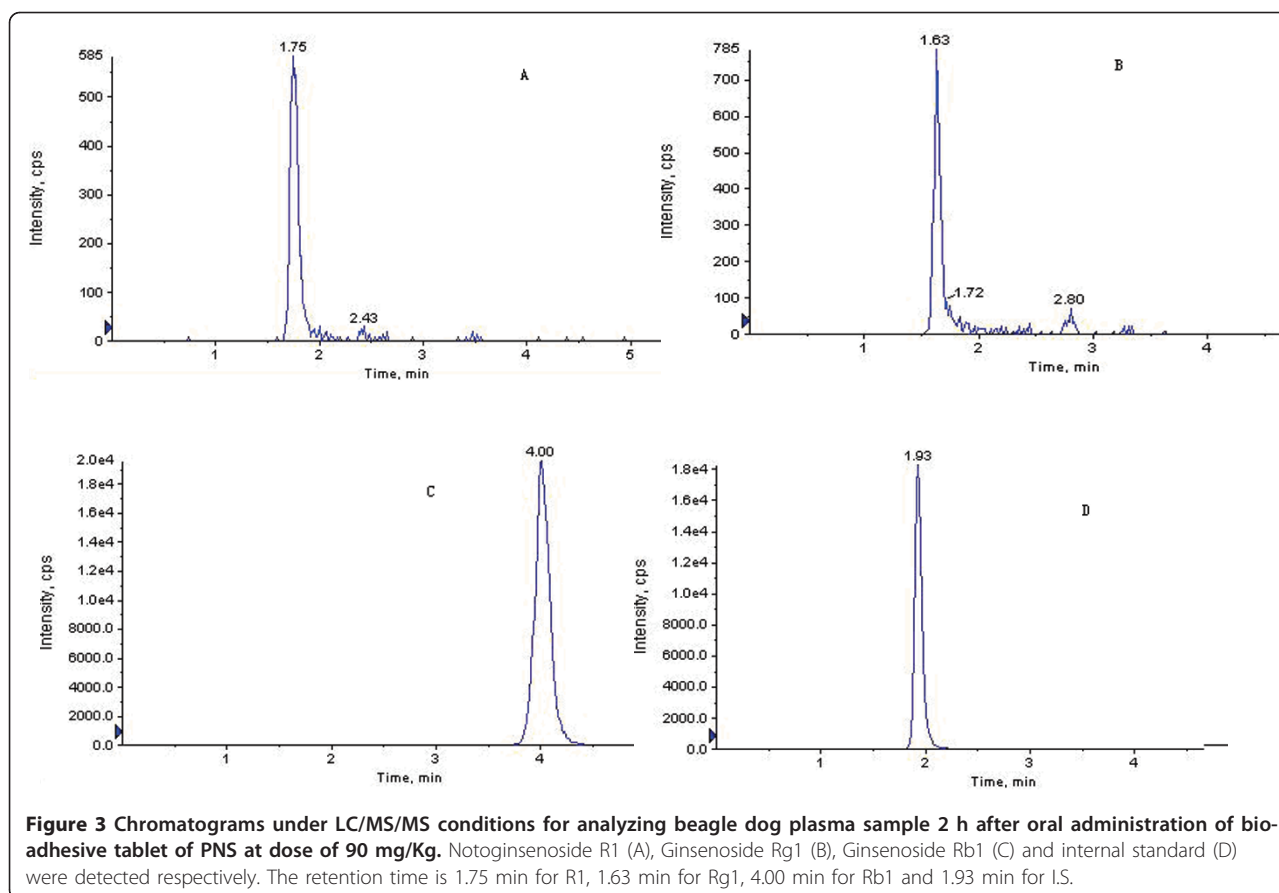
Figure 2 Chromatograms under LC/MS/MS conditions for analyzing beagle dog plasma spiked with Notoginsenoside R1 (A), Ginsenoside Rg1 (B), Ginsenoside Rb1 (C) and internal standard gliplizide (D). MS/MS transitions monitored in the positive ion mode were from m/z 1007 to m/z 423 for R1 (MW 932), from m/z 875 to m/z 423 for Rg1 (MW 800), from m/z 1183 to m/z 487 for Rb1 (MW 1108), and from m/z 494 to m/z 369.1 for internal standard. Intensity cps: ion intensity is in counts per second. The retention time is 1.67 min for R1, 1.56 min for Rg1, 3.81 min for Rb1 and 1.86 min for I.S.

study, we investigated the pharmacokinetics property of PNS in dogs, which is useful to prefigure its potential efficacy when it is administered to human being. The concentration-time curves of three components of six dogs were shown in Figure 5. All three concentration-time curves of bio-adhesive tablet of PNS shared a similar multiple-peak phenomenon. Our result was inconsistent with Xu's report [12], in which the rats' concentration-time curves of Rg1 and Rb1 were single-peak. In Xu's report, they failed to detect Rg1 in rats' serum after 24h, while we detected R1, Rg1 and Rb1 till 72h. The reason of this inconsistency might be the differences of administrating doses, analytical methods and formulation modifications between the previous and present studies. In our study, 90 mg/kg PNS tablet was orally administered to beagle dogs while the dose of PNS in documental reports was 600 mg/kg. Owing to our improved analytical method, the PNS blood concentration could be detected at nanogram level compared to the microgram level of Xu's report. By virtue of the improvement of our more sensitive detection method,

we could reveal more veritable pharmacokinetics properties of PNS after oral administration.

Specifically, there were several potential factors contributed to multiple-peak phenomenon showed in all three ingredients' results: Because of the gastric emptying effect, drug got to small intestine where it was primarily absorbed nonsynchronously and hence entered the blood at different time; PNS was absorbed at different positions in gastrointestinal tract and each position had different absorption rate; Enterohepatic circulation: the two or more peaks occurred in three concentration-time curves might be caused by the hydrolytic effects of some bacterial enzymes or the influence that bile released intermittently during the process of re-absorption of PNS; Moreover, according to previous pharmacokinetics research, R1, Rg1 and Rb1 had a great distribution in several organs, especially in kidney, heart and liver [17-19]. Thus their redistribution effect might also be another possible cause for the multiple-peak phenomenon occurred in our study.

When we compared the pharmacokinetics property of Rb1 with R1 and Rg1, we found that there were more



peaks in Rb1's concentration-time curve than that of R1 and Rg1. Besides, we detected high concentration of Rb1 in plasma till 72h, while the concentrations of the other two ingredients in plasma are quite low after 36h. It can be inferred that several possible reasons besides those we had discussed above may combine together to account for the different pharmacokinetics property of Rb1: In Han's research, the protein-binding rate in plasma for Rb1 (80.11~89.69%) was considerably higher than Rg1(6.56~12.74%), the protein-binding effect could prolong the existence of Rb1 in plasma, and the process that Rb1 dissociated from protein in plasma to release uncombined ingredient maybe related with more peaks in Rb1's concentration-time curve. Moreover, Rb1 might be absorbed in colon. Although previous study reported that Rb1 was degraded evidently in large intestine [20], chitosan was able to improve the stability of PNS, especially Rb1, due to its ability to improve the distribution of intestinal microorganisms, to inhibit the biological synthesis at the surface of bacteria's cell membrane and damage the transmission of energy crossed through it. Based on such mechanisms, chitosan reduced the degradation of Rb1 and enabled it to be absorbed in colon. Additionally, other ingredients in PNS might affect the

absorption of Rb1. Considering of the experimental condition and animal-protectionism, we only used 6 beagle dogs in this study. So it was unreasonable to deny the possibility of individual difference between dogs as well as its influence on the result of our pharmacokinetics study. Using more beagle dogs might enable the result more persuasive, but it was not covered by this current study. The pharmacokinetics property of Rb1 was very complex and should be subjected to further study.

3.3. The relative bioavailability and other pharmacokinetics parameters

The parameters of AUC for R1, Rg1 and Rb1 between normal tablet and bio-adhesive tablet were increased remarkably ($P < 0.05$), and the relative bioavailability after oral administration of bio-adhesive tablets is 204.53% for R1, 152.73% for Rg1 and 150.50% for Rb1. This result (Table 1) indicates that bio-adhesive formulation considerably improved the oral bioavailability of PNS. The parameter of T_{max} for R1, Rg1 and Rb1 was significantly increased ($P < 0.05$). The parameter of C_{max} for R1 and Rb1 between normal tablet and bio-adhesive tablet was increased remarkably ($P < 0.05$), which reveals that there was a process of accelerating release

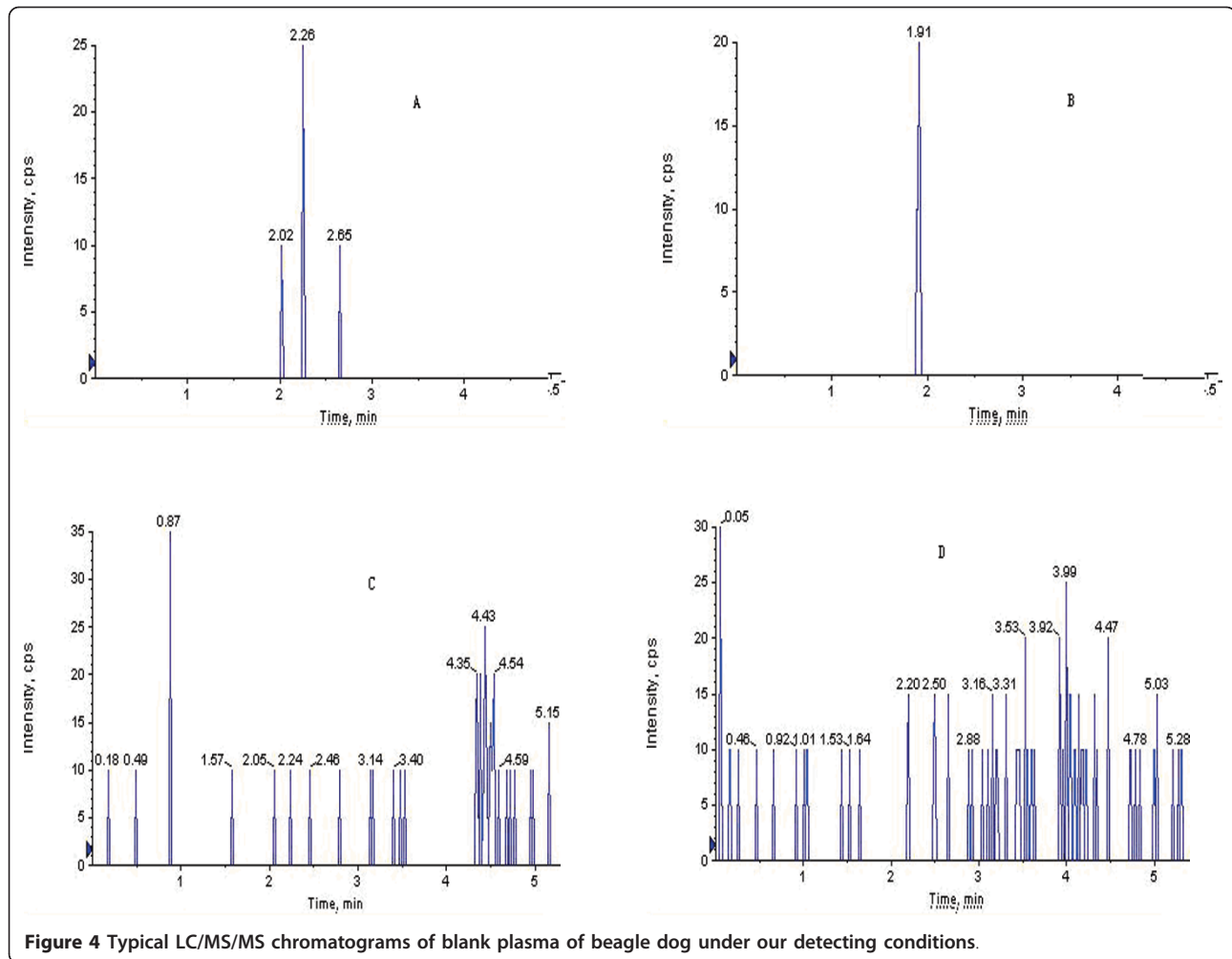


Figure 4 Typical LC/MS/MS chromatograms of blank plasma of beagle dog under our detecting conditions.

or improving assimilation. Though there was no statistical difference of C_{max} for Rg1 between two kinds of tablet, its MRT was significantly prolonged from 6.40h to 11.54h ($P < 0.05$), which indicated that the improvement of AUC of Rg1 was attributable to a prolonged assimilation and slow release. It can be inferred that the increase of MRT for Rg1 was probably the result of prolonging drug's residence time in gastrointestinal tract based on chitosan's specific properties of polymeric cationic, gelling and adhesivity. Chitosan's expansibility *in vivo* might retard the release of Rg1, and Rg1's high protein-binding rate in liver maybe another possible reason.

The improvement of AUC for R1 and Rb1 were more likely a consequence of increasing permeation of drug through intercellular space by reducing the transmembrane electric resistance of epidermal cell. The permeation might be further increased by the electrostatic interaction between positively charged chitosan and negative charged cell membrane. The different spatial structures of three components might also

account for the different mechanisms upon which they relied to enhance AUC.

The formulation modification of bio-adhesive tablet using chitosan might be closely related with the changes of pharmacokinetics properties of PNS. Chitosan was applied in our study based on its unique advantages: 1. Low oral toxicity and good biocompatibility that guarantee sufficient safety for using. Chitosan was degraded into low molecular oligosaccharide by lysozyme or NAG, such product cannot accumulate in internal environment. The final degradation product glucosamine was able to be absorbed by the organism [21-23]; 2. Property to control or prolong drug's release: the viscous property and expansibility of chitosan enabled it to retard the release of PNS [24]; 3. Increasing permeation of drug through intercellular space: chitosan was able to open the cell junction and to influence the mucous membrane reversibly [25]; 4. Improving drug's stability in gastrointestinal tract: PNS was surrounded by chitosan and thus was protected against damage in acid environment of gastrointestinal tract [26]. According to some

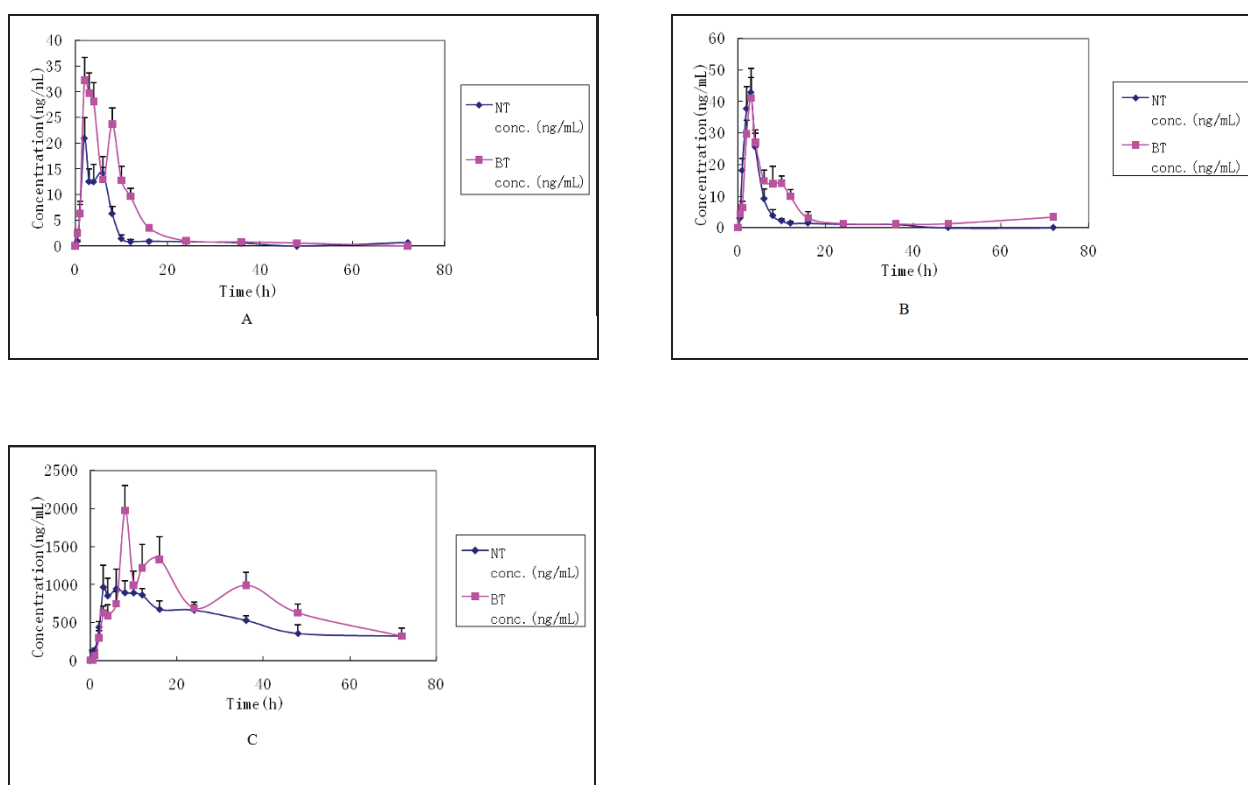


Figure 5 Mean concentration-time profiles of Noto Ginsenoside R1 (A), Ginsenoside Rg1 (B) and Ginsenoside Rb1 (C) in beagle dog plasma after oral administration of two types of tablets, Normal tablet (NT) and Bio-adhesive tablet (BT). The dose of oral administration of PNS is 90 mg/kg (n = 6).

reports, Rg1 and Rb1 were unstable in gastric fluid [27-29], 90% Rg1 and 80% Rb1 were degraded after 2 hours incubation in simulated gastric fluid [30]. The amino group of chitosan could interact with acidic components and then neutralized excessive gastric acid, thereby reducing the damaging effect PNS encountered in stomach and enhancing its bioavailability.

Conclusions

In this study we used chitosan as a bio-adhesive material to prepare a modified formulation in order to improve

the bioavailability of PNS after oral administration, the experimental result has revealed that our bio-adhesive tablet has significantly enhanced the bioavailability of PNS in beagle dogs, which indicates that this kind of formulation is helpful to improve the therapeutic effect of PNS and conducive to expand its clinical application.

Abbreviations

LC-MS/MS: liquid chromatography-tandem mass spectrometry; HPLC: high-performance liquid chromatography; SPE: solid-phase extraction; MRM: Multiple reaction monitoring; IS: internal standard; LOQ: limit of quantification; RSD: Relative standard deviation; BT: bio-adhesive tablet; NT: normal tablet.

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Authors' contributions

FHZ processed and interpreted the data, performed the statistical analysis and drafted and critically revised the manuscript; CW carried out the pharmacokinetics study; ZCY conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Table 1 Pharmacokinetic parameters of Noto Ginsenoside R1, Ginsenoside Rg1 and Rb1 after oral administration of PNS normal and bio-adhesive tablets (50 mg/kg) to dogs (n = 6)

	R1		Rg1		Rb1	
	NT	BT	NT	BT	NT	BT
Tmax(h)	2.67	5.00*	2.33	3.33*	9.33	10.67*
Cmax(ng/mL)	27.83	47.69*	55.58	42.03	1090.45	2448.90*
MRT(h)	9.93	9.19	6.40	11.54*	26.38	26.68
AUC(ng/mL)Sh	132.11	270.21*	199.08	304.06*	35579.73	53546.15*

NT: normal tablet; BT: Bio-adhesive tablet

* P < 0.05 versus oral administration of normal tablet.

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