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Stability of Xuesaitong capsules in gastrointestinal lavage fluid

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Abstract *Objective:* To obtain a formulation with high bioavailability through evaluation of the stability of three types of Xuesaitong capsules in the stomachs and intestines of rats. We compared the stability of the Panax notoginsenoside R_1 as well as the ginsenosides Rg_1, Rb_1, Re, and Rd in different formulations.
Methods: Artificial stomach fluid (ASF) and artificial intestinal fluid (AIF) were prepared. Stability of three types of Xuesaitong capsules was examined for 4 h in stomachs and 24 h in intestines. Samples were analyzed at different times by high-performance liquid chromatography. Percent content of NGR_1, GRg_1, GRb_1, GRe, and GRd at different times was calculated.
Results: Hard capsules incubated in ASF disintegrated within 2—3 min, whereas soft capsules disintegrated within 7—8 min. Components in hard capsules were dissolved rapidly in water, with content of each compound reaching 90% in 5 min, and degradation of each compound reaching 30—50% after incubation for 240 min. Dissolution and degradation of each component in soft capsules with a water-soluble base tended to balance at 30—90 min. Contents in soft capsules with a lipid-soluble base showed slow dissolution after ASF incubation for 120 min. Five saponins in identical types of capsules incubated in ASF had similar stability curves. Contents of hard capsules and soft capsules with a water-soluble base degraded rapidly within 30 min and reached a plateau when Xuesaitong capsules were incubated in AIF.

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Conclusions: Contents of capsules with a lipid-soluble base degraded slower than the other two types of capsules incubated in ASF and AIF, suggesting that they may have better bioavailability.

Introduction

Xuesaitong is a traditional Chinese herbal formula in capsule form used to promote blood circulation and dilate blood vessels. As such, in China, the formula is used for the treatment of coronary heart disease, angina, stroke, paralysis and other cardiovascular/cerebrovascular diseases. Studies have shown that Xuesaitong capsules can reduce platelet aggregation, increase blood flow, improve hemodynamics,[1] improve neurologic deficiency[2,3] and improve symptoms of coronary heart disease and angina.[4]

Main active components of Xuesaitong formula are *Panax notoginseng* saponins (PNS). Protopanaxatriol-type saponins such as NGR_1, GRg_1, and GRe can be metabolized to protopanaxatriol, which is absorbed into blood via oral administration. Our previous studies showed differences in peak blood concentrations of protopanaxatriol for three types of Xuesaitong capsules after oral administration in beagle dogs. Protopanaxadiol-type saponins GRb_1 and GRd were absorbed poorly through oral administration,[5] and the absolute bioavailability of GRb_1 was only 0.26%. Oral dosage forms of PNS can be metabolized by enzymes and intestinal flora.

We examined the stability of three types of Xuesaitong capsules incubated in the stomachs and intestines of rats. We compared the stability of NGR_1, GRg_1, GRb_1, GRe, and GRd in different formulations to obtain a formulation with high bioavailability.

Materials and methods

Materials

The PNS R1, the ginsenosides Rg_1, GRg_1, Rb_1, Re, and Rd, and standards were obtained from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Sodium chloride was purchased from Beijing Chemical Reagents (Beijing, China). Pepsase and trypsase were obtained from Cytoskeleton (Denver, CO, USA). High-performance liquid chromatography (HPLC)-grade acetonitrile was from MREDA Technology (Beijing, China). Ultrapure water was generated from a Synergy ultraviolet water-purification system (Millipore, Billerica, MA, USA). Xuesaitong capsules (batch number: 20111023) were obtained from Yunnan Weihe Pharmaceuticals (Yunnan, China). Xuesaitong soft capsules (batch number: 20121017 163) were purchased from Kunming Flame Pharmaceuticals (Kunming, China), as were Xuesaitong soft capsules with a batch number of 13109-10.

Table 1 Gradients of the mobile phase.

Time (min)	Phase A (%, acetonitrile)	Phase B (%, water)
0	19	81
25	19 → 45	81 → 55
50	45 → 55	55 → 45
55	55 → 19	45 → 81
60—70	19	81

Animals

Male Sprague—Dawley rats (220—250 g) were purchased from Vital River Laboratories (Beijing, China). Rats were fasted for 24 h but had unlimited access to water before experimentation.

Animal experiments were undertaken in accordance with the *Guidelines for the Care and Use of Laboratory Animals* (US National Institutes of Health, Bethesda, MD, USA). The study protocol was approved by the Animal Experimentation Committee of the Beijing University of Chinese Medicine (Beijing, China).

Method validation

HPLC conditions

PNS were analyzed by HPLC using a Extend-C18 column (4.6 mm × 250 mm, 5 μm; Agilent Technologies, Santa Clara, CA, USA) and a pre-column (WATCH Y164; Agilent Technologies) with ultraviolet detection ($\lambda = 203$ nm). The mobile phase was acetonitrile and water and eluted according to values shown in Table 1. The mobile phase was pumped at 1.5 mL/min at 37°C, and the injection volume was 20 μL.

Table 2 Linear relationship between NGR_1, GRg_1, GRb_1, GRe and GRd ($n = 6$).

Constituent	Regression equation	r	Linearity range (mg/L)
NGR_1	$Y = 2.2789X - 9.4934$	0.9999	5.2—104.0
GRg_1	$Y = 2.5522X - 21.7050$	0.9999	12.5—250.0
GRe	$Y = 2.2698X - 6.8187$	0.9999	2.2—44.0
GRb_1	$Y = 1.8148X - 9.3990$	0.9999	11.9—238.0
GRd	$Y = 2.2023X - 1.2172$	0.9999	2.6—52.0