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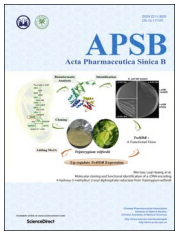

ORIGINAL ARTICLE

Self-microemulsifying drug delivery system for improving the bioavailability of huperzine A by lymphatic uptake

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Lymphatic transport

Abstract Huperzine A (Hup-A) is a poorly water-soluble drug with low oral bioavailability. A self-microemulsifying drug delivery system (SMEDDS) was used to enhance the oral bioavailability and lymphatic uptake and transport of Hup-A. A single-pass intestinal perfusion (SPIP) technique and a chylomicron flow-blocking approach were used to study its intestinal absorption, mesenteric lymph node distribution and intestinal lymphatic uptake. The value of the area under the plasma concentration–time curve (AUC) of Hup-A SMEDDS was significantly higher than that of a Hup-A suspension ($P<0.01$). The absorption rate constant (K_a) and the apparent permeability coefficient (P_{app}) for Hup-A in different parts of the intestine suggested a passive transport mechanism, and the values of K_a and P_{app} of Hup-A SMEDDS in the ileum were much higher than those in other intestinal segments. The determination of Hup-A concentration in mesenteric lymph nodes can be used to explain the intestinal lymphatic absorption of Hup-A SMEDDS. For Hup-A SMEDDS, the values of AUC and maximum plasma concentration (C_{max}) of the blocking model were significantly lower than those of the control model ($P<0.05$). The proportion of lymphatic transport of Hup-A SMEDDS and Hup-A suspension were about 40% and 5%, respectively, suggesting that SMEDDS can significantly improve the intestinal lymphatic uptake and transport of Hup-A.

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1. Introduction

Self-microemulsifying drug delivery systems (SMEDDS), as a type of lipid-based oral drug delivery system, can significantly enhance the oral bioavailability of poorly water-soluble drugs[1]. SMEDDS may affect drug absorption in many ways, including enhancing drug solubilization, increasing membrane permeability in the gastrointestinal tract, and increasing lymphatic drug uptake[2,3]. Water-insoluble drugs can be transported into the systemic circulation through the intestinal lymphatic system without first-pass metabolism in the liver and so can increase the oral bioavailability[4]. Lymphatic uptake has been proven to be an important factor to increase the oral bioavailability of numerous highly lipophilic drugs, including halofantrine[5], moxidectin[6], dichlorodiphenyltrichloroethane (DDT)[7,8], probucol[9], cyclosporine A[10], lycopene[11], saquinavir[12] and puerarin[13,14].

The absorption of drugs in the intestine is a fundamental aspect of oral administration. The absorption rate constant (K_a) and the apparent permeability coefficient (P_{app}) reflect the extent of intestinal drug absorption[15]. The single-pass intestinal perfusion (SPIP) model is used to determine drug concentration in intestinal perfusion fluid from the perfused intestinal segment, and it can directly describe the intestinal drug absorption[16].

In the study of lymphatic drug transport, the lymph duct-cannulated approach is the most direct method to investigate intestinal lymphatic drug uptake. However, this method requires a high level of surgical skill and the rate of success is low. In recent years, an indirect pharmacological method (named "chylomicron flow-blocking approach") has been used to evaluate intestinal lymphatic drug transport. This method utilizes the intestinal chylomicron flow inhibitors Pluronic-L81 and cycloheximide to study intestinal lymphatic transport[17]. Numerous studies have proven that measurement of lymphatic drug absorption using the chylomicron flow blocking approach correlates well with the lymph duct-cannulated approach[13,18–20].

Huperzine A (Hup-A), an alkaloid, is extracted from the traditional Chinese medicine *Huperzia serrata* (Thunb.) Trev[21]. Hup-A is a poorly water-soluble drug, easily soluble in methanol and ethanol, but insoluble in water. Thus, the present study was to prepare and characterize a SMEDDS formulation of Hup-A and to investigate the effect of Hup-A SMEDDS on intestinal absorption, mesenteric lymph nodes distribution, and intestinal lymphatic uptake with comparison to a Hup-A suspension, utilizing the SPIP approach and a chylomicron flow-blocking approach.

2. Materials and methods

2.1. Materials

Huperzine A (purity 99%) was purchased from Wanbangde Pharmaceutical Group Co., Ltd. (Zhejiang, China). Diphenhydramine hydrochloride (Lot No. 100066–200807) was purchased from the National Institutes for Food and Drug Control (Beijing, China). Propylene glycol was obtained from Tianjin Damao Chemical Reagent Factory (Tianjin, China). Polyoxyl 40 hydrogenated castor oil (Cremophor RH40®) was purchased from BASF, Germany. Castor oil was obtained from Sinopharm Group Chemical Reagent Co., Ltd. (Shanghai, China). Cycloheximide was purchased from Sigma Chemical Co. (St. Louis, MO, USA). Acetonitrile and methanol were HPLC grade and were supplied by the Oceanpak Alexative Chemical Co., Ltd. (Gothenburg, Sweden). Pure water was prepared by the Milli-Q Ultrapure water purification system (Millipore, Bedford, MA, USA). All other chemicals used in this study were analytical grade.

2.2. Preparation of Hup-A formulations

The composition of the SMEDDS was based on that used in our previous study with some modifications[22], *i.e.*, Hup-A SMEDDS was composed of castor oil (16%, *w/w*), Cremophor RH40 (50%, *w/w*) and propylene glycol (34%, *w/w*). Preparation of Hup-A SMEDDS was by simply mixing these components. Hup-A was initially dissolved in propylene glycol followed by dropping Cremophor RH40 and castor oil at room temperature until a homogeneous mixture formed. The mixture was stored overnight at room temperature. It subsequently was examined for signs of turbidity or phase separation before evaluation. The Hup-A suspension was prepared by dissolving Hup-A in 0.5% (*w/v*) sodium carboxymethyl cellulose (CMC-Na) solution by ultrasonication.

2.3. Characterization of the Hup-A-loaded self-microemulsion

The Hup-A SMEDDS was diluted 100-fold with distilled water and mixed by gentle shaking. Zetasizer Nano 3690 (Malvern Instruments Ltd., UK) was used to measure the particle size and zeta potential of the microemulsion at 25 °C[23]. Transmission electron microscopy (TEM; H-7650; Hitachi, Tokyo, Japan) was used to determine the morphology of microemulsion. After Hup-A SMEDDS was diluted 100-fold with distilled water, the sample was stained with 2% (*w/v*) phosphotungstic acid aqueous solution (PTA) for 5 min at 25 °C. Then one drop of stained sample was placed on a copper grid. After drying, it was examined under the TEM[24].

2.4. Bioavailability study

Sprague-Dawley rats (male, 210–260 g; Center of Experimental Animals, Anhui, China; certificate No. SCXK (Wan) 2011-002) were utilized for all bioavailability and absorption studies. Animal experiments were performed according to the guidelines of our institution for the care and use of laboratory animals in Anhui University of Chinese Medicine (Hefei, China), and conformed to the National Institutes of Health Guide for Care and Use of Laboratory Animals. All surgeries were performed under sodium pentobarbital anesthesia, and every effort was made to minimize suffering. The rats were fasted for 12 h with free access to water, and were divided into two groups at random before the experiments. The rats were administered a single oral dose of the Hup-A

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