Acta Pharmaceutica Sinica B 2014;4(1):86–93

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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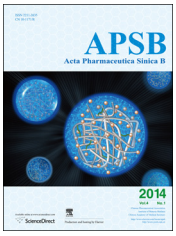

ORIGINAL ARTICLE

Preparation and evaluation of sustained-release solid dispersions co-loading gastrodin with borneol as an oral brain-targeting enhancer

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Received 5 December 2013; revised 11 December 2013; accepted 27 December 2013

KEY WORDS

Borneol;
Gastrodin;
Oral drug delivery;
Brain-targeting;
Gastric mucosa irritation;
Sustained-release

Abstract Borneol is a traditional Chinese medicine that can promote drug absorption from the gastrointestinal tract and distribution to the brain. However, stomach irritation may occur when high doses of borneol are used. In the present work, gastrodin, the main bioactive ingredient of the traditional Chinese drug "Tianma" (Rhizoma Gastrodiae) was used as a model drug to explore reasonable application of borneol. Sustained-release solid dispersions (SRSDs) for co-loading gastrodin and borneol were prepared using ethylcellulose as a sustained release matrix and hydroxy-propyl methylcellulose as a retarder. The dispersion state of drug within the SRSDs was analyzed by using scanning electron microscopy, differential scanning calorimetry, and powder X-ray diffractometry. The results indicated that both gastrodin and borneol were molecularly dispersed in an amorphous form. Assay of *in vitro* drug release demonstrated that the dissolution profiles of gastrodin and borneol from the SRSDs both fitted the Higuchi model. Subsequently, gastric mucosa irritation and the brain targeting of the SRSDs were evaluated. Compared with the free mixture of gastrodin and borneol, brain targeting of SRSDs was slightly weaker (brain targeting index: 1.83 *vs.* 2.09), but stomach irritation obviously reduced. Sustained-release technology can be used to reduce stomach irritation caused by borneol while preserving sufficient transport capacity for oral brain-targeting drug delivery.

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Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

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http://dx.doi.org/10.1016/j.apsb.2013.12.012

1. Introduction

In many compounds employed in traditional Chinese medicine (TCM), a so-called messenger drug is usually included. It is capable of introducing the main effective drugs in the prescription to the target site to increase therapeutic efficacy[1–3]. The bicyclic monoterpene borneol (Fig. 1A) is one such messenger drug that is frequently used in the treatment of encephalopathy like stroke, epilepsy and headache. Studies have shown that borneol can promote drug absorption from the gastrointestinal tract and facilitate distribution to the brain[4–8]. However, stomach irritation may occur when a high dose of borneol is used[9,10], which limits the clinical application of borneol as an oral brain-targeting enhancer.

Gastrodin (*p*-hydroxymethylphenyl-*β*-D-glucopyranoside, Fig. 1B), the main bioactive ingredient of the traditional Chinese drug "Tianma" (Rhizoma Gastrodiae), is used in the treatment of some central nervous system disorders, such as vertigo, headache, insomnia, neuralgia, neurasthenia and epilepsy in TCM[11–13]. Gastrodin has attracted increasing attention because of its low toxicity and therapeutic efficacy. Gastrodin acts on the brain to produce central inhibitory effects, but it does not easily pass through the blood–brain barrier (BBB) due to its hydrophilicity. In fact, the drug concentration in brain after administration is far lower than in other tissues[14,15]. Enhancing the delivery of gastrodin to the brain could improve therapeutic efficacy.

Our previous work indicated that 400 mg/kg of borneol can accelerate the absorption of gastrodin (200 mg/kg) in mice gastrointestinal tract and promote its distribution to the brain[4]. In this study, gastrodin was still used as a model drug to explore reasonable application of borneol as an oral brain-targeting enhancer. Sustained-release technology is one of the efficient methods for decreasing stomach irritation by drugs[16,17]. The solid dispersion technique using water-insoluble carriers can be used to sustain the drug release and reduce drug side effects[18]. A sustained-release solid dispersion (SRSD) medium was designed for co-loading gastrodin with borneol. The SRSDs were prepared using ethylcellulose (EC) as a sustained-release matrix and hydroxypropyl methylcellulose (HPMC) as a retarder. The physicochemical characterization, levels of gastric mucosa irritation, and brain targeting effect of borneol on gastrodin within the SRSDs was evaluated.

2. Materials and methods

2.1. Materials and animals

Synthetic borneol was purchased from Guangzhou Chemical Industrial Co. (Guangzhou, China). Gastrodin (purity 99.7%) was synthesized and analyzed for purity by Kunming Pharmaceutical Co. (Kunming, China). Ethylcellulose (EC, 100 cp) and hydroxy-propyl methylcellulose (HPMC, K100M) were kindly provided by Shanghai Colorcon Coating Technology Co., Ltd. (Shanghai, China). Gastrodigenin (purity 99.5%) was purchased from Dingxin Chemical Industrial Co. (Yizheng, China). Hydroquinone (purity 99.4%) was purchased from Sanjili Chemical Industrial Co. (Lianyungang, China) and used as the internal standard solution (100 μg/mL in methanol). Water was deionized and double distilled. Other chemical reagents were of chromatographic or analytical grade and commercially available.

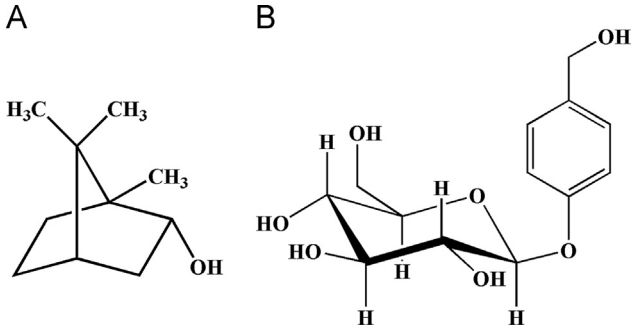

Figure 1 Chemical structures of borneol (A) and gastrodin (B).

Healthy male Sprague-Dawley rats (230–270 g) and male Kunming strain mice (18–22 g) were obtained from the Laboratory Animal Center of Southern Medical University (SCXK 2006-0015, China). Prior to experimentation, animals were acclimated for at least 1 week to a 12 h light/dark cycle with free access to standard chow and water. The animals were fasted overnight but supplied with water *ad libitum* before the experiments. All experimental protocols were approved by the Institutional Animal Care and Use Committee of Southern Medical University.

2.2. Preparation of the SRSDs

The SRSDs were prepared by conventional solvent evaporation method. Gastrodin, borneol, EC and HPMC at a weight ratio of 1:2:4:1 were mixed and dissolved in a minimum volume of ethanol in a beaker. The solvent was removed at 30 °C in a vacuum oven until there was no alcohol smell. The dried dispersion was kept in refrigerator (−20 °C) for 2 days to harden. The resultant solid dispersions were pulverized with a mortar and pestle, sieved to obtain 40–60 mesh particles, and then stored in a desiccator at room temperature.

2.3. Scanning electron microscopy

Representative scanning electron microscope (SEM) images of the samples, including the physical mixture of drugs with excipients and the SRSDs, were taken using a JSM-5900LV SEM (Jeol, Tokyo, Japan) at 20 kV acceleration voltage without Au or Pt coating. For the SEM observations, each sample was fixed on an aluminum sample holder using double-side carbon tape.

2.4. Differential scanning calorimetry

The thermal behavior of drug formulations are important in pharmaceutical technologies, since the obtained information such as melting, recrystallization, decomposition, or a change in heat capacity could help to ascertain the physicochemical status of the entrapped drug inside the excipient. Differential scanning calorimetry (DSC) measurements were performed using a DSC-Q100 (TA instruments, New Castle, DE, USA). The DSC thermograms were collected from a 3 mg sample held in a sealed aluminum pan. The thermograms were generated at a heating rate of 20 °C/min from 0 to 270 °C with nitrogen purge at 50 mL/min. An empty aluminum pan was used as reference.

2.5. Powder X-ray diffractometry

In order to determine whether the drugs were amorphous or crystalline within the formulation, powder X-ray diffractometry (PXRD) study was conducted for the pure drug, the polymers, the