Saudi Journal of Biological Sciences (2016) 23, S113–S125

King Saud University

Saudi Journal of Biological Sciences

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Improvement of oral availability of ginseng fruit saponins by a proliposome delivery system containing sodium deoxycholate

Fei Hao [a], Yanxi He [a], Yating Sun [a], Bin Zheng [a], Yan Liu [a], Xinmei Wang [b], Yongkai Zhang [c], Robert J. Lee [a,b], Lirong Teng [a,*], Jing Xie [a,*]

[a] College of Life Sciences, Jilin University, Changchun, Jilin 130012, China
[b] College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA
[c] The Firest Hospital of Jilin University, Changchun, Jilin 130012, China

Received 10 July 2015; revised 10 September 2015; accepted 14 September 2015
Available online 9 October 2015

KEYWORDS

Ginseng fruit saponins;
Proliposomes;
Sodium deoxycholate;
Oral bioavailability;
Pharmacokinetics

Abstract Ginseng fruit saponins (GFS) extracted from the ginseng fruit are the bioactive triterpenoid saponin components. The aim of the present study was to develop a drug delivery system called proliposome using sodium deoxycholate (NaDC) as a bile salt to improve the oral bioavailability of GFS in rats. The liposomes of GFS were prepared by a conventional ethanol injection and formed the solid proliposomes (P-GFS) using *spray drying* method on mannitol carriers. The formulation of P-GFS was optimized using the response surface methodology. The physicochemical properties of liposome suspensions including encapsulation efficiency, *in vitro* drug release studies, particle size of the reconstituted liposome were tested. The solid state characterization studies using the method of Field emission-scanning electron microscope (FE-SEM), Fourier transform infrared (FT-IR) and Differential scanning colorimetric (DSC) were tested to study the molecular state of P-GFS and to indicate the interactions among the formulation ingredients. *In vitro* studies showed a delayed release of ginsenoside Re (GRe). *In vivo* studies were carried out in rats. The concentrations of GRe in plasma of rats and its pharmacokinetic behaviors after oral administration of GFS, Zhenyuan tablets (commercial dosage form of GFS) and P-GFS were studied using ultra performance liquid chromatography tandem mass spectrometry. It was founded that the GRe concentration time curves of GFS, Zhenyuan tablets and P-GFS were much more different in rats. Pharmacokinetic behaviors of P-GFS showed a second absorption peak on the concentration time curve. The

* Corresponding authors at: School of Life Sciences, Jilin University, Room 352, Life Science Building, Jilin University, No. 2699, Qianjin Street, Changchun 130012, China (J. Xie).
E-mail address: xiejing@jlu.edu.cn (J. Xie).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.sjbs.2015.09.024

pharmacokinetic parameters of GFS, Zhenyuan tablets, P-GFS in rats were separately listed as follows: T max 0.25 h, C max 474.96 ± 66.06 ng/ml and $AUC_{0-\infty}$ 733.32 ± 113.82 ng/ml h for GFS; T max 0.31 ± 0.043 h, C max 533.94 ± 106.54 ng/ml and $AUC_{0-\infty}$ 1151.38 ± 198.29 ng/ml h for Zhenyuan tablets; T max 0.5 h, C max 680.62 ± 138.051 ng/ml and $AUC_{0-\infty}$ 2082.49 ± 408.33 ng/ml h for the P-GFS. The bioavailability of P-GFS was nearly 284% and 181% of the GFS and Zhengyuan tablets respectively. In conclusion, the proliposomes significantly enhanced the drug bioavailability, absorption in the gastrointestinal tract and decreased its elimination time of GRe in rats and could be selectively applied for oral delivery of GFS.

1. Introduction

Ginseng (panax ginseng) is a highly used and valued Chinese herbal medicine to treat a variety of ailments for thousands of years. Saponins extracted from the ginseng plant are the active compounds and responsible for most of the pharmacological effects of ginseng. Ginseng fruit saponins (GFS) extracted from the berry of Ginseng possess higher ginsenoside contents than the roots and recently are a hotspot in treating many diseases (Yang et al., 2010). GFS are a group of the dammarane-type triterpene saponins. In previous publications, it had been proved that GFS showed a positive bioactivity effect in atherosclerosis, anti-diabetic and anti-obesity effects, diabetes associated cognitive deficits, anti-inflammatory activity, histamine and cytokine release, anti-stress effect, and systemic lupus erythematosus (Attele et al., 2002; Huo, 1984; Park et al., 2012; Yang and Zhang, 1986; Zhang and Jiang, 1981; Zhang et al., 1984). Ginsenoside Re (GRe) which contains the structural backbone of protopanaxatriol is the most important major bioactivity constituents of GFS and has been chosen as the character for evaluation of GFS (Lee et al., 2014). In particular, a previous study showed that ginsenoside Re in ginseng berry extracts showed a superior oral absorption of ginsenoside Re at equivalent ginsenoside Re dose to pure ginsenoside Re, indicating that GFS might be a good form for ginsenoside Re intake (Joo et al., 2010).

GFS is well-known as the *BCS III* (Biopharmaceutics Classification system) drugs with high solubility and low permeability. The poor oral bioavailability was observed for its low permeability and fast degradation and clearance in the gastrointestinal tract (Kim et al., 2013; Peng et al., 2012). To improve bioavailability of GFS, a variety of formulations such as nano particle, phospholipid complex, liposome have been used in previous studies (Ajazuddin and Saraf, 2010). Phospholipids have the characteristics of excellent biocompatibility and amphiphilicity. These unique properties make phospholipids most appropriate to be employed as important pharmaceutical excipients (Li et al., 2015). And the lipid-based drug delivery systems enhance the intestinal drug permeability and solubility (Larsen et al., 2011; Porter et al., 2008; Trevaskis et al., 2008). Liposomes can entrap both hydrophilic and hydrophobic agents, which could protect the entrapped agents from external destructive conditions, such as light, pH and enzymes (Chen, 2008).In addition to the property of liposome adhesion to and absorption into the intestinal epithelial cells, liposome as a novel method was used to improve the bioavailability of GFS. Considering the poor physicochemical stability problems of liposome including aggregation, fusion, oxidation and active agent's leakage, one effective approach is used to formulate the aqueous liposome into solid proliposome defined as dry, free-flowing particles, containing water soluble carrier particles coated with phospholipids (Yanamandra et al., 2014). Once contacted with water, proliposome could immediately form a liposomal dispersion and be more uniform in size. The methods of preparing proliposome include single step *spray drying* method (Patil-Gadhe and Pokharkar, 2014), vacuum evaporation (Janga et al., 2012; Keon-Hyoung Song and Chang-Koo Shim, 2002), film deposition method (Janga et al., 2012), and fluidized bed method (Chen and Alli, 1987). The *Spray drying* method was used in this study considering the application in industries. Some studies focusing on proliposome surface charge and Carboxymethyl chitosan coated modification were reported to further improve the absorption of liposomes in the gastrointestinal tract (Bai et al., 2011; Janga et al., 2012). A liposome containing bile salts called *bilosomes* is widely studied and is a hotspot to biocompatibility compared with surface charge (Senior, 2001). *Bilosomes* have been applied to the oral immunization of peptide and protein antigens (Conacher et al., 2001) and could improve the integrity and stability of oral liposomes in gastrointestinal media (Hu et al., 2013). The enhanced oral absorption of *bilosomes* could be achieved by improving *in vivo* residence time, and permeation across the biomembranes and trans-endocytosis internalization has been reported in a previous study (Niu et al., 2014). Sodium deoxycholate (NaDC) had been used as a bile salt to improve absorption and stability of vesical particles for the drug application dosages in oral delivery system (Gangadhar et al., 2014).

In the present study, the P-GFS containing sodium deoxycholate was firstly prepared and optimized to improve the oral bioavailability of the GFS. The physicochemical properties and the molecule state of the proliposomes were characterized by methods of FE-SEM, DSC and FT-IR. Particle size, encapsulation efficiency, stability evaluation, *in vitro* drug release and *in vivo* bioavailability studies in rats of P-GFS were also investigated to evaluate in this delivery system.

2. Materials and methods

2.1. Materials

Ginseng fruit saponins (GFS) were gifted from Bo Xiang Pharmaceutical Group (Ji Lin, China). Egg yolk phosphatidylcholine (EPC) with the purity over 80%, was purchased from the Guangzhou hanfang modern Chinese medicine