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Abstract

Development and Characterization of Self-emulsifying Drug Delivery Systems (SEDDS) of Angelica oil and Zedoary Turmeric oil

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Radix Angelicae Sinensis (Danggui in Chinese, DG), the dried rhizome of *Angelica Sinensis* (Oliv.) Diels of Umbelliferae herb, grows widely in Gansu province. Because that it could nourish blood, regulate menstruation and relieve pain, so it was praised as "ten prescriptions with nine danggui in" in Chinese medicine. At the present, more than 70 compounds have been isolated and identified from DG, and nearly half of them belong to the essential oil. In Chinese pharmacopoeia (2005), ferulaic acid, which is a hydrophilic compound, is used as the quality control component for DG. Although the essential oil is not regarded as the quality control components for DG, many pharmacological and clinical studies indicated that coniferyl ferulate (CF), *E/Z*-ligustilide (*E/Z*-lig) and *E/Z*-butylidenephthalide (*E/Z*–bp) are considered as the main bioactive components in DG oil, which could inhibit platelet aggregation, relax uterus and tracheal muscle, prevent gynecological disease and treat menstrual disorders etc. Among of them, *Z*-ligustilide has been paid much attention because of its relatively high content in DG oil (more than 30%) as well as its well established preventive and therapeutic effect on cardiovascular and cerebrovascular diseases.

Curcuma zedoaria Rosc. (Ezhu in Chinese) was the dried rhizome of *Curcuma phaeocaulis* Val., *Curcuma kwangsiensis* S. G. Lee et C. F. Liang, *Curcuma. Wenyujin.* Y. H. chen et C. Ling. Ezhu could guide "qi" downward, promote blood flow, remove food retention and relieve pain. The essential oil of Ezhu, also named as

Zedoary Turmeric Oil (Ezhu oil), is extracted from the herb and consisted of many bioactive components. In Chinese pharmacopeia (2005), germacrone is utilized as the quality control component in Ezhu oil. Pharmacological and clinical studies indicated that the main six active components in essential oil are neocurdione (NCD), curdione (CD), germacrone (GM), curzerene (CZ), furanodiene (FD) and β-elemene (β-E), which have anti-tumor, relieve pain, promote blood flow, remove the necrotic tissue and strengthen immune capability of the organism.

Based on the previous research of Danggui and Ezhu oil, the objectives of the present study are to develop and characterize the self-emulsifying drug delivery systems (SEDDS) for above two essential oils. Moreover, pharmacokinetics study of SEDDS of Ezhu oil was also conducted in rat.

The content of each chapter is organized as follows:

1. Isolation and purification of *Z*-ligustilide from Danggui oil

The volatile component *Z*-ligustilide was purified from total essential oil of Danggui by middle-pressure column chromatography and identified by GC-MS with the purity of ~98%. The prepared *Z*-ligustilide was used as the standard compound in the following studies.

2. Development of SEDDS of Danggui and Ezhu oil

Pseudo-ternary phase diagrams were constructed to identify the efficient self-emulsification regions. Each preparation was characterized in terms of emulsification time, droplet size and zeta potential after dispersion into water to determine the optimal formulation, which was further subjected to dissolution and stability evaluation. DG oil could serve as a partial oil phase with the aid of the second oil phase and the combined use of the surfactants produced better self-emulsifying microemulsions. Increasing the surfactant concentration reduced the droplet size but increased the emulsification time, while the reverse effect was observed by increasing the cosurfactant concentration. The optimized formulation consisted of DG oil, ethyl oleate, Tween 80, Labrasol and Transcutol (16:24:38.5:16.5:5, w/w) with droplet size of 56.2±4.2 nm and ζ-potential of -42.4±3.7 mV. Similar results were also obtained for SEDDS of Ezhu oil. The optimized formulation consisted of Ezhu oil, ethyl oleate, Tween 80 and Transcutol (30.8:7.7:40.5, w/w) with droplet size of 68.3±1.6 nm and ζ-potential of -41.2±1.3 mV. The emulsification times for above two developed SEDDS were all below 1 min.

3. Characterization of SEDDS of Danggui and Ezhu oil

The active components (e.g. *E/Z*-lig and *E/Z*-bp for DG oil; NCD, CD, GM, CZ, FZ and βE in Ezhu oil) could be rapidly released (> 85%) from the optimized SEDDS in aqueous media (e.g. water, PBS buffer or 0.1N HCl) and remained stable in intact SEDDS for at least 12 months (DG SEDDS) or 9 months (EZhu SEDDS) at room temperature.

4. Pharmacokinetics study of SEDDS of Ezhu oil

Formulated SEDDS of Ezhu oil and original Ezhu oil were orally administrated to SD rat. The concentrations of the germacrone (GM) in rat plasma were quantified by HPLC-DAD. The results showed that compared with Ezhu oil, the bioavailability of developed SEDDS of Ezhu oil increased to 175.38%. Moreover, the C_{max} significantly increased to about 2 times with a shorter time to reach the peak concentration ($p<0.05$).

Keywords: *Radix Angelicae Sinensis* (Danggui); *Curcuma Zedoaria Rosc.* (Ezhu); Essential oil; Zedoary Turmeric Oil; Self-emulsifying drug delivery systems (SEDDS); Microemulsion; Pseudo-ternary phase diagrams; Droplet size; Zeta potential, Dissolution; Stability; Bioavailability