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Abstract

Improved Quality Evaluation for Danshen Products and Formulation Study on a Lipophilic Component (Tanshinone IIA) in Danshen

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Danshen (*Salvia miltiorrhiza*) is a commonly used traditional Chinese medicine for the treatment of cardiovascular and cerebrovascular diseases. In China, numerous pharmaceutical products of Danshen are commercially available, which include tablets, capsules, granules, injectables and oral liquids etc. In the Chinese Pharmacopeia (2005), only salvianolic acid B and tanshinone IIA were determined by HPLC method as quality control markers. And no dissolution and stability tests were required. The objective of this study was to apply the improved quality evaluation method to evaluate the quality of Danshen products. Considering both hydrophilic and lipophilic active components, danshensu, protocatechuic aldehyde, salvianolic acid B, cryptotanshinone and tanshinone IIA were selected as five markers. A HPLC method was developed to simultaneously determine their contents, which were used to compare the products from different companies, and different batches from the same company. Similarity factor method was used to evaluate the similarities of in-vitro dissolution profiles. Moreover, accelerated and long-term stability tests were performed to predict the shelf-life of Danshen products. Results showed that all of the Danshen products passed the content requirements of Chinese pharmacopeia. However, the content variations of the hydrophilic components were much higher

than those of the lipophilic components. In dissolution tests, most of the hydrophilic components were dissolved completely while all of the lipophilic components could not be detected. The f_2 values showed that there were no similar dissolution profiles among different brands of Danshen products. Contents of the five markers decreased by the first-order kinetic processes in the accelerated and long-term stability tests. The predicted shelf-life of Danshen products were shorter than those labeled on the products. It was suggested that more markers with defined content range instead of lower content limit are required for better control of Danshen products. Dissolution and stability tests need to be added into the quality control criteria in the Chinese Pharmacopeia.

Among the components isolated from Danshen, Tanshinone (TanIIA) is a major lipophilic and thermosensitive bioactive diterpenoid for the treatment of myocardial infarction and myocardial ischemia. However, TanIIA has very poor oral absorption (<5%), which may be due to its poor dissolution rate, low permeability across the intestinal membrane, intensive first-pass metabolism and interaction with efflux transporters. In this study, TanIIA was formulated with Flouric68 (F68), PEG4000 and polyvinylpyrrolidone (PVP40) to prepare solid dispersions by Spray-Freezing Drying (SFD) technology for the inhancement of its aqueous dissolution profile. Powder X-ray diffraction (PXRD) patterns showed that the intensities of characteristic peaks of TanIIA dramatically decreased in TanIIA/F68 and TanIIA/PVP SFD products compared to the unprocessed TanIIA. Scanning electron microscopy (SEM) micrographs also displayed that SFD products appeared lacking of crystallinity while TanIIA was styloid crystals. Fourier transform infrared spectroscopy (FTIR) spectrum revealed that the interactions between TanIIA and excipients were the evidence for the changed PXRD and SEM profiles. Dissolution results exhibited that SFD products with TanIIA/F68 (1:9,w/w) has a higher dissolution rate to about 70%. In an animal study which compared oral absorption of SFD products of TanIIA/F68-1:9 to unprocessed TanIIA group (n=4), C_{max} of SFD products was significantly increased to 2.4- and 1.4-fold for unchanged and total TanIIA after enzyme hydrolysis, respectively ($p < 0.05$). However, AUC and MRT did not significantly increase ($p > 0.05$) compared to those of the control. In conclusion, SFD technology is feasible for preparing TanIIA SFD products with amorphous structure, larger surface area and higher dissolution rate. However, the pharmacokinetic profiles indicated the

dissolution process might not be the rate-limiting step for the absorption of TanIIA in vivo.

Keywords: Danshen; Quality Evaluation; Dissolution; Stability; Tanshinone IIA (TanIIA); Spray-Freezing Drying (SFD) Technology; Characterization; Absorption; Pharmacokinetics