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Original Research Paper

Improved dissolution and bioavailability of silymarin delivered by a solid dispersion prepared using supercritical fluids

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ABSTRACT

The objective of this study was to improve the dissolution and bioavailability of silymarin (SM). Solid dispersions (SDs) were prepared using solution-enhanced dispersion by supercritical fluids (SEDS) and evaluated *in vitro* and *in vivo*, compared with pure SM powder. The particle sizes, stability, and contents of residual solvent of the prepared SM-SDs with SEDS and solvent evaporation (SE) were investigated. Four polymer matrix materials were evaluated for the preparation of SM-SD-SEDS, and the hydrophilic polymer, polyvinyl pyrrolidone K17, was selected with a ratio of 1:5 between SM and the polymer. Physicochemical analyses using X-ray diffraction and differential scanning calorimetry indicated that SM was dispersed in SD in an amorphous state. The optimized SM-SD-SEDS showed no loss of SM after storage for 6 months and negligible residual solvent (ethanol) was detected using gas chromatography. *In vitro* drug release was increased from the SM-SD-SEDS, as compared with pure SM powder or SM-SD-SE. *In vivo*, the area under the rat plasma SM concentration-time curve and the maximum plasma SM concentration were 2.4-fold and 1.9-fold higher, respectively, after oral administration of SM-SD-SEDS as compared with an aqueous SM suspension. These results illustrated the potential of using SEDS to prepare SM-SD, further improving the biopharmaceutical properties of this compound.

Abbreviations: HPMC, hydroxypropyl methylcellulose; PVP, polyvinyl pyrrolidone; SD, solid dispersion; SE, solution evaporation; SEDS, solution-enhanced dispersion by supercritical fluids; SM, silymarin.

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1. Introduction

Silymarin (SM), an extract of *Silybum marianum* (L.), contains a mixture of four flavonolignan isomers: silibinin (70–80%), silycristin (20%), silydianin (10%), and isosilybin (0.5%) [1,2]. Silybin is therefore the major component of SM and is responsible for its pharmacological activity. SM has traditionally been self-administered for the treatment of liver disorders [3,4]. The effects of SM on the liver have been attributed to its inhibition of hepatotoxin binding to receptor sites on the hepatocyte membrane; inhibition of glutathione oxidation, increasing its levels in the liver and intestine; antioxidant activity; and stimulation of ribosomal RNA polymerase and subsequent protein synthesis, leading to enhanced hepatocyte regeneration [5]. However, the effectiveness of SM as a liver disease remedy is limited by its poor aqueous solubility, resulting in low oral bioavailability due to poor enteral absorption [6]. Recently, various vehicles have been employed to improve the solubility and bioavailability of SM, such as solid lipid nanoparticles, microemulsion systems, liposomes, and solid dispersions (SDs) [7–10].

SDs have been used widely to enhance the dissolution rate of drugs with low aqueous solubility. In SD systems, a drug may exist as an amorphous form within a polymeric carrier. This may result in an increased drug dissolution rate, as compared with its crystalline form. The mechanisms involved in this SD-mediated enhancement of drug dissolution have been proposed by several investigators [11,12].

SDs can be prepared using a range of methods, such as melting, solvent evaporation, solvent melting, spray-drying, and supercritical fluid techniques. Supercritical fluid approaches have several advantages over more conventional preparation methods, including the ability to reduce residual organic solvent levels and to produce SDs with smaller particle sizes and better flowability [13]. There are several variants of supercritical fluid techniques, including rapid expansion of supercritical solutions, particles from gas-saturated solutions, gas antisolvent process, supercritical anti-solvent process, precipitation from compressed anti-solvent, aerosol solvent extraction system, and solution-enhanced dispersion by supercritical fluids (SEDS). SEDS provides the most promising method for the preparation of SD [14]. It uses semi-continuous processes to atomize the solution into a supercritical atmosphere. Provided that the drug is sparingly soluble in the supercritical fluid, which is highly soluble in the solvent, the supercritical fluid in the solvent droplets can produce an antisolvent effect. This process produces super-saturated solutions, facilitating precipitation of the solid in the form of small particles [15].

In the current study, SEDS was used to establish an SD delivery system for oral administration of SM, with the aim of enhancing drug dissolution and bioavailability. The physicochemical properties of SD prepared using several polymer materials were investigated, including polyvinyl pyrrolidone (PVP) K17, PVP K30, hydroxypropyl methylcellulose (HPMC) K4M, and HPMC K15M. In addition, analyses of stability and residual solvent were performed to compare SM-SD prepared by SEDS and by solvent evaporation (SE). *In vitro* dissolution and *in vivo* pharmacokinetics were analyzed to assess the SM-SD-SEDS.

2. Materials and methods

2.1. Materials

SM (purity >80%) and PVP K17 were purchased from Dalian Meilun Biotech Co., Ltd. (Dalian, China). PVP K30 was obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). HPMC K4M and HPMC K15M were supplied from Colorcon (USA). Carbon dioxide (CO_2) with a purity of 99.99% was obtained from Shanghai Jiao Tong University (Shanghai, China). All other chemicals were reagent grade and used as received.

2.2. Animals

Animal studies of male Wistar rats weighing 250 ± 10 g were conducted with the approval of the Animal Ethical Committee, Shanghai University of Traditional Chinese Medicine. The animals were kept in an agreeable environment with free access to a rodent diet and water and were acclimatized for at least 1 week before the start of the study.

2.3. Preparation of SM-SD

The supercritical pilot plant at Nantong Huaxing Petroleum Devices Co., Ltd. (Nantong, China), shown in a schematic diagram in Fig. 1A, was employed in this study. Briefly, this apparatus included three major components: a CO_2 delivery system, an organic solution delivery system, and a precipitation system. The supercritical CO_2 and the organic solution were separately pumped into the high pressure vessel through different inlets of the coaxial nozzle (the diameter of inner tubule was 0.2 mm and diameter of outside part was 1 mm) and continuously discharged from the bottom. The inner structure of the nozzle is shown in Fig. 1B. For preparation of SM-SD, CO_2 from the cylinder (Fig. 1A, 1) was refrigerated (2) and compressed to 15 MPa by the high-pressure pump (3) before the temperature controlling system (6) was activated to increase the temperature to 50 °C. The pressure of the precipitation system was increased by injection of CO_2 until the pressure reached 15 MPa. After the pressure and temperature of the view vessel (9) reached the required values, valve C was adjusted to maintain constant pressure in the vessel. Then SM and the excipients with the weight ratio of 1:5 (based on the results of preliminary experiment) were separately dissolved or dispersed in ethanol and a mixture of dichloromethane and ethanol (3/2, v/v). The solution was aspirated by a high pressure constant flow pump (11) (LC100, Nantong, China) at a flow rate of 1 ml/min. Supercritical CO_2 and the organic solution mixed and diffused rapidly. Solutes originally dissolved in the organic solvent rapidly reached super-saturation, resulting in the precipitation of SM-SD-SEDS in the vessel. Once the solution was exhausted, valve B was closed, and supercritical CO_2 was continuously pumped for about 40 min in order to remove residual organic solvent from the SM-SD. After that, valve A was closed while valve C remained open. The pressure of the precipitation vessel was slowly reduced and the product in the vessel was collected for further use.