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Original Research Paper

Enhanced water-solubility of Licorice extract microparticle prepared by antisolvent precipitation process

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ABSTRACT

In this study, Licorice extract (LE) microparticles were successfully prepared using antisolvent precipitation process. Ethyl acetate and dimethyl sulfoxide, were used as the antisolvent and solvent, respectively. By means of orthogonal experimental design, the influences of several process parameters on the mean particle size (MPS) were investigated. The concentration range of the LE solution, the volume ratio of solvent to antisolvent, dripping speed, and temperature were 4.3–34.5 mg/mL, 1:1–1:12, 1–10 mL/min, and 20–35 °C, respectively. Based on the above orthogonal experiments, the optimum antisolvent precipitation process conditions were found to be: temperature 20 °C, concentration of the LE solution 17.2 mg/mL, volume ratio of solvent to antisolvent 1:4, dripping speed 10 mL/min. The LE microparticles were characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), Fourier transform-infrared (FT-IR) spectroscopy, thermal gravimetric analysis (TG), differential scanning calorimetry (DSC), HPLC analysis and dissolution test. And the morphology, crystalline state and chemical structure, drug purity, dissolution rate and bioavailability of LE microparticles were investigated. Under optimum antisolvent precipitation process conditions, the MPS of LE microparticles reached to 85.3 nm, and with uniform distribution. And the LE microparticles had the same chemical structure as the unprocessed drug, but the crystallinity was reduced, purity was increased. Furthermore, the water solubility increased from 4.82 mg/mL to 16.10 mg/mL, and bioavailability is increased by 64.36%.

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1. Introduction

Licorice is commonly used in China as herbal medicine, mainly distributed in the north, northeast and northwest regions [1]. Glycyrrhizic acid (GA) and Licorice flavonoids are two main components in Licorice extract, their structure are shown in Fig. 1. Glycyrrhizic acid, the highest content of in liquorice extract, has anti-inflammatory [2–5], anti-viral [6,7], anti-fungal [8], anti-oxidation activity [9,10], anti-angiogenic activities [11] and is a clinically effective drug for the hepatitis treatment [12–14]. Glycyrrhetinic acid has antitumor activity [15,16]. Licorice flavonoids has antioxidant and anti-inflammatory activities [17]. Licorice extract can reduce lipopolysaccharide-induced inflammation [18].

However, due to the low water solubility of glycyrrhizin and Licorice flavonoids, the feature greatly reduces the efficacy of oral formulations bioavailability. In order to solve this problem, many scientists have done related research. The representative methods include GA liposome [14,19–22], glycyrrhetinic acid liposome [22–24], GA-chitosan nanoparticles delivery system [25–28], GA-supercritical anti-solvent process [29] and Licorice flavonoids-supercritical anti-solvent process [30]. But they are the ways to carry raw material medicine and nanocrystallize the monomer medicine, not liquorice extract.

One way to improve the solubility is to reduce its diameter by the preparation techniques of drug powder. Generally, ball milling [31] and grinding method were employed to transform the size of the single active components in Licorice. Although they can achieve drug particle size, high energy consumption, low efficiency, particle size distribution width, easy pollution, insecurity, easy degradation and destruction of drugs and other shortcomings make them unsuitable to pharmaceutical industry. Supercritical anti-solvent process and antisolvent precipitation are advanced preparation methods of nanodrug. But supercritical anti-solvent method is high cost, complicated operation and not easy to scale production. Antisolvent precipitation process changes drug saturation solubility and brings about re-crystallization process. So compared with other drug micronization methods, the antisolvent process has the advantages of low cost, simple operation, easy to scale and industrialization. Now, anti-solvent precipitation method for nanometer drug monomer preparation, include GA study on supercritical anti-solvent process [29] and Licorice flavonoids

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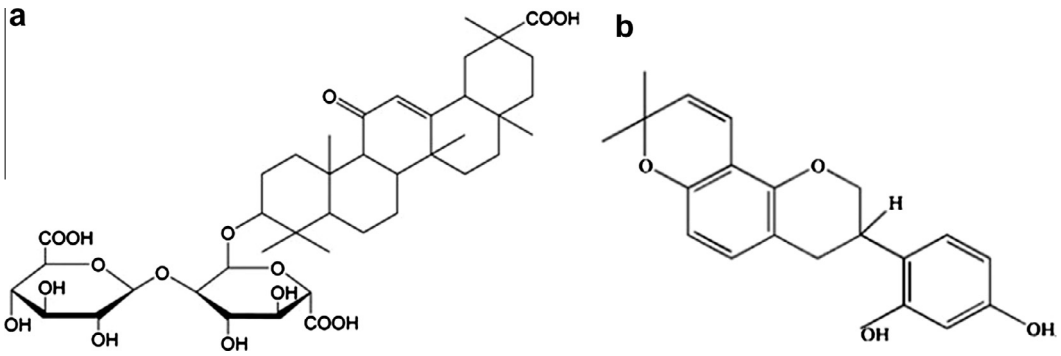

Fig. 1. Chemical structure of main component in Licorice extract. (a) Glycyrrhizic acid; (b) Licorice flavonoid.

study on supercritical anti-solvent process. There is not any report about nano LE study.

This research aims to prepare LE microparticles by antisolvent precipitation process. Orthogonal design experiments were employed to obtain the optimal preparation conditions. And the morphology, crystalline state and chemical structure, drug purity, dissolution rate and bioavailability of LE microparticles were investigated.

2. Materials and methods

2.1. Materials

Licorice extract, (LE, GC content 20%) was purchased from Tongtai plant chemical Co., Ltd. (Si Chuan, PR China). Reference compound of GA (⩾98%) was purchased from J&K Chemical Ltd. (Beijing, China). Dimethyl sulfoxide (DMSO), ethyl acetate and other reagents obtained from Beijing Chemical Reagents Co. (Beijing, China) were of analytical grade. HPLC-grade methanol and acetonitrile were from Sigma. Deionized water was purified by a Milli-Q water purification system from Millipore (Bedford, MA, USA).

2.2. Preparation of LE microparticles

LE microparticles was prepared by the antisolvent precipitation technique. Briefly, a certain amount of LE was completely dissolved in 2 mL DMSO solvent in the beaker, was ultrasonicated for 5 min, centrifuged at 10,000 r/min for 5 min and supernatant was taken. Using a peristaltic pump, the LE solution was then injected into certain multiple volumes of antisolvent ethyl acetate under stirring. The bath temperature was set at room temperature. Precipitation of solid drug particles occurred immediately upon mixing. After a certain time, the suspension was centrifuged at 5000 rpm for 10 min, left a layer of precipitation. Repeatedly with ethyl acetate was washed for 3–4 times through repeated centrifugation. The particles were oven-dried at 70 °C for 8 h or freeze-dried. Every experiment was repeated at least three times. The preparation schematic diagram of anti-solvent process was shown in Fig. 2.

2.3. Optimization of antisolvent precipitation process

An $OA_{16}(4^5)$ orthogonal experiment was chosen for optimization of the operating conditions for LE microparticle by the antisolvent precipitation process. The antisolvent precipitation process optimization experiment was carried out with four factors and four levels. The range of each factor level was based on the results of preliminary experiments. The concentration range of the LE solution, the volume ratio of solvent to antisolvent, dripping speed, and temperature were 4.3–34.5 mg/mL, 1:1–1:12, 1–10 mL/min, and 20–35 °C, respectively. The factors and levels of the OAD are shown in Table 1. The MPS of LE microparticle was variable dependent. LE microparticle was obtained from the above 16 tests (Table 2). The Design-Expert version 7.0 software was applied to analyze the statistical experimental design. The significance level is stated at 95%, with a p value of 0.05.

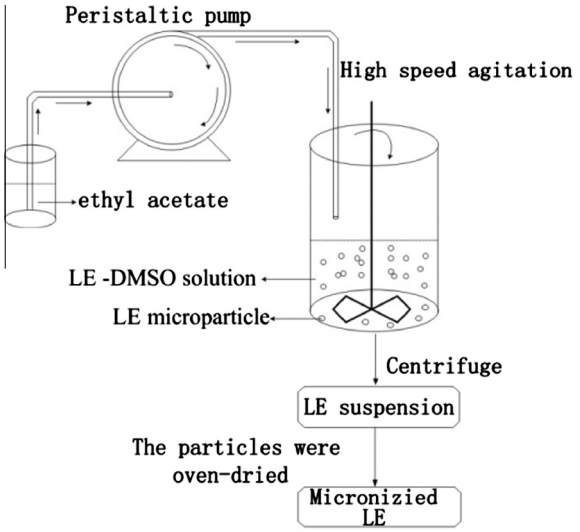

Fig. 2. Preparation schematic diagram of anti-solvent process.

Table 1
Factors and levels of the OAD.

	A Temperature (°C)	B Concentration of LE solution (mg/mL)	C Volume ratio of solvent to antisolvent	D Dripping speed (mL/min)
1	20	34.5	1:1	1
2	25	17.2	1:4	4
3	30	8.6	1:8	7
4	35	4.3	1:12	10

2.4. Particle characterization

2.4.1. Particle size analysis

Number average particle diameters and number average particle size distribution of the prepared LE microparticles were measured by dynamic light scattering (DLS) using particle size analyzer laser (ZetaPALS, Brookhaven Instruments Co., USA). The

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