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Preparation and pharmacokinetic study of fenofibrate cubic liquid crystalline

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ABSTRACT

An LCC delivery system for Fenofibrate (Fen) was developed to improve its poorly oral bioavailability. Fen-LCC preparation methods were screened, and the prepared Fen-LCC was then characterized by a polarizing microscope and transmission electron microscopy (TEM). The spray drying technique was selected to dry and solidify particles into powder. The *in vitro* release of Fen-LCC was measured and *in vivo* pharmacokinetic experiments were carried out on rats after oral administration. Particles prepared through the high-temperature input method exhibited structural characteristics of LCC, and re-dissolved particles maintained the same features. The LCC delivery system can significantly improve *in vitro* release outcomes. After oral administration, AUCs of the suspension and LCC systems were measured at 131.6853 μg·h/ml and 1435.72893 μg·h/ml, respectively. The spray drying process presented here better maintains cubic structures, and the LCC system significantly improves bioavailability levels.

1. Introduction

Fenofibrate (Fen) is a phenoxyaromatic acid that can regulate blood lipid levels [1]. After administration, Fen is hydrolyzed by esterases of tissues and plasma, generating the bioactive metabolite fenofibric acid (Fefa) and thus playing a role in reducing blood lipid levels.

Fen is a lipophilic compound that is almost insoluble in water with an oil/water distribution coefficient of 5.3, resulting in its poor oral absorption. Therefore, the bioavailability of oral Fen administration is very low [2,3]. The solubility must

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be improved in order to increase its bioavailability *in vivo*. Solubilized nanoparticles have clinical defects such as poor physical and chemical stability, so that it would be difficult to practice in the normal situations [4]. The development direction of nanoparticle is to solidify the nanoparticles, then to redissolve and re-structure them. Therefore, spray drying and freeze drying technologies are extensively applied in the solidification of nanoparticles, among which freeze drying technology would cost too much and does not suit the industrial production. Fen preparations used in foreign and domestic markets include capsules and tablets, and the micronization of bulk drugs is the most commonly used approach. In addition, other dosage modes (e.g., double-layer osmotic pump preparation [5], delayed-release micropellets [6], nanosuspension and micronized capsules of Fen) have been reported in the literature. However, due to solubility limitations, certain factors restrict the improvement of its bioavailability.

In this study, a high-temperature input method was applied to prepare Fen lipid cubic liquid crystalline (LCC) particles. Worle's results [7,8] indicate that non-cubic will transfer to cubic during autoclaving of the dispersions. Given the advantages of this unique "honeycomb" structure (the closed-lipid-bilayer structure composed of dual-consecutive water and lipid layers) and the large membrane surface area it provides, LCC can increase the solubility of Fen, thereby improve its bioavailability. The obtained Fen-LCC microparticles were spray-dried and solidified into the powder for the ease of administration, transport and carrying.

2. Materials and methods

2.1. Materials

Fen raw material (Wuhan Galaxy Chemical Co., Ltd., Hubei, China); Fen standard (Batch No: 200401, National Institute for Food & Drug Control, Beijing, China); glycerol monooleate (GMO, Aladdin, Shanghai, China); poloxamer 407 (F127, Badische Anilin- und Soda-Fabriken Co., Ltd., German).

SYQ DSX 280B Autoclave (Shanghai Shenan Medical Instrument, Shanghai, China); XSP-8CA Polarizing Microscope (Shanghai Optical Instrument Factory No. 6, Shanghai, China); JEM-2010HR Transmission Electron Microscope (JEOL Co., Ltd., Japan); L-117 Mini-Lab Spray Dryer (Beijing Laiheng Science&Trade Co., Ltd., Beijing, China); Zetasizer Nano ZS90 Laser Particle Size Analyzer (MALVEM, England); LC-20AB HPLC (Shimadzu International Trading Co., Ltd., Shanghai, China); UH-S2 Ultrasound Cells Crusher (AUTO SCIENCE Technology Co., Ltd., Taiwan, China); ZRD6-B Drug Dissolution Instrument (Shanghai Huanghai Pharmaceutical Instrument Factory, Shanghai, China).

SD rats, weighed 250 ~ 300 g, without gender limitations, were provided by Animal Center, Guangzhou University of Chinese Medicine, Certificate of Conformity: SCXK (Yue) 2008-0020. All animal procedures were approved by the Animal Ethics Committee of Guangdong Pharmaceutical University.

2.2. LCC preparation

First, 20 g GMO and 2 g F127 were melted in a 60 °C water bath, and then 1 g Fen was added, melted and mixed into an 80 °C water bath; 30 min of sonication was then performed to form a uniform blend; 50 ml of distilled water was then added to the mixture and processed under high pressure levels and 121 °C for 15 min; the mixture was then subjected to Ultrasound Cells Crusher treatment for 30 min to shrink it to a nanometer-size stable state [9]. After the above procedures, a stable dispersion of Fen-LCC was successfully prepared.

2.3. LCC precursor preparation

2.3.1. Spray dry precursor preparation

The prepared Fen-LCC was added to 12.42% maltodextrin and then diluted with water (1:10) for the following spray drying procedure. The spray drying conditions were as follows: the inlet air temperature was set to 130 °C, the actual outlet temperature was set to 97~90 °C, the wind speed was set to 90 cm/sec, and the feeding rate was set to 35 ml/min. Spray drying generated white spray-dried Fen-LCC powder.

2.3.2. Determination of in vitro release

Three copies of 100 mg Fen raw materials (100 mesh) and spray-dried Fen-LCC powder (including 100 mg Fen) were tested for *in vitro* release. We used 500 ml of 1% SDS solution as the releasing medium, and the test was performed at 37 °C and 100 rpm. We sampled 4 ml of solution at the 0, 1st, 3rd, 5th, 7th, 9th and 11th h, and 4 ml of fresh releasing medium was added at the same time. The solution was filtered through a 0.45 μm pore membrane to discard the initial filtrate, and the subsequent filtrate was collected, from which 20 μl was injected into HPLC for determination [10,11]. The detection wavelength was measured at 286 nm, and the mobile phase was methanol-water (82:18). The column temperature was measured at 30 °C with a flow rate of 1.0 ml/min. Peak areas were used to calculate concentrations at different time points.

2.4. Polarizing microscope observations of Fen-LCC

Nine different GMO: H_2O-ratio groups were selected, namely: 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80 and 10:90. Fen and GMO ratios were selected uniformly from 6:94 to 1:99 [12]. GMO was mixed with F127 at a ratio of 10:1 and then melted in a 60 °C water bath. The melted mixture was added to a corresponding proportion of Fen and then melted and mixed into an 80 °C water bath and sonicated for 30 min to achieve uniformity. A high pressure treatment was then applied at 121 °C for 15 min [13], generating a stable dispersion of Fen-LCC. The above stable LCC dispersion with different dosages of Fen was applied in droplets onto a slide for observation under a polarizing microscope.

2.5. TEM characteristic observation

A droplet of Fen-LCC sample solution was distributed onto a glass slide covered in a copper mesh with formvar support film. After being left to stand for 1.5 min, excessive liquid has been absorbed and the copper mesh had dried; 2 droplets of 2% tungstophosphoric acid hydrate ($H_3(PO_4W_{12}O_{36}) \cdot 14H_2O$, pH = 7) were then added onto the slide and covered with the sample slide for 1.5 min of negative staining. The copper mesh was

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