Original article

Effect of superfine pulverization on physicochemical and medicinal properties of Qili Powder

Guowei Zhao\textsuperscript{a,b}, Xinli Liang\textsuperscript{a}, Chunliu Wang\textsuperscript{c}, Zhenggen Liao\textsuperscript{a,}\textsuperscript{*}, Zhiwei Xiong\textsuperscript{a}, Zhe Li\textsuperscript{a}

\textsuperscript{a}Key Laboratory of Modern Preparation of Traditional Chinese Medicine, Ministry of Education, JiangXi University of Traditional Chinese Medicine, Nanchang, China
\textsuperscript{b}Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi’an, China
\textsuperscript{c}Shannxi Academy of Traditional Chinese Medicine, Xi’an, China

ARTICLE INFO

Article history:
Received 14 July 2014
Accepted 6 September 2014

Keywords:
Medicinal properties
Physicochemical properties
Qili Powder
Superfine pulverization

ABSTRACT

Qili Powder, a preparation from Traditional Chinese Medicine, commonly used to treat injuries from falling or stumbling, pain caused by bruising, and traumatic hemorrhage. The aim of the present work was to investigate the application of the superfine pulverization on Qili Powder properties. The physicochemical and medicinal properties of fine Qili Powder with D\textsubscript{90} particle size of 164.5 μm, and superfine Qili Powder with D\textsubscript{90} particle size of 32.2 μm were investigated. The results showed that with decreasing particle size, the specific surface area and pore volume increased, the fluidity decreased, and the percentage of moisture absorption and the balanced moisture content decreased. Analysis HPLC, XRD and FTIR results indicated that superfine pulverization didn’t influence dracorhodin content, nor the molecular structure and crystal form of Qili Powder. The percentage of dissolution of dracorhodin was significantly improved after superfine pulverization. Pharmacokinetics results confirmed that superfine pulverization increases the absorption rate in rats and dracorhodin content of Qili Powder.

© 2014 Sociedade Brasileira de Farmacognosia. Published by Elsevier Editora Ltda. All rights reserved.

Introduction

Traditional Chinese medicine (TCM) has more than 2000 years of history in the prevention and treatment of diseases in China (Li et al., 2008), and it plays an indispensable role in the Chinese healthcare system. In TCM, several different herbs are mixed into a preparation due to their own properties and to be therapeutically effective as a whole. This type of compatible application of herbs in TCM exhibits holistic effectiveness by exerting activities to multiple target organs (organ systems) on the basis of the principles of traditional oriental medicine (Ma et al., 2009). The pharmacological effects of TCM do not only depend on the special chemical components but also the physical states of drugs. In TCM, many medicinal materials are orally administered directly after grounding into a powder. The powders’ particle size affects their pharmaceutical behavior, such as solubility; yield of chemical constituents, chemical stability, bioavailability and among others. It was...
found that the water holding capacity and polysaccharide solubility significantly improved with the decrease in size of *Astragalus membranaceus* particles ($p < 0.05$) (Zhao et al., 2010). It was reported that after superfine pulverization, the plant cell walls of Bai Zhi are broken into pieces and the extraction yield of imperatorin increased by 11.93% compared with the normal particles (Yang et al., 2011). Su (Su et al., 2009) studied the effect of ultrafine grinding on dissolving-out quantity of tanshinone IIA from *Radix Salvia miltiorrhiza*, and the results indicated that the molecular structure of the active ingredients did not change, the dissolving-out quantity of tanshinone IIA increased greatly from 12.77 μg/g to 54.55 μg/g. It was found that ultrafine grinding can obviously increase the absorption rate and degree of absorption of Liuwei Dihuang in rats (Ma et al., 2009). Previous investigations from our group showed that loose ultrafine grinding can obviously increase the absorption rate of dracorhodin from *Liuwei Dihuang* in rats (Ma et al., 2009, 2010). Su (Su et al., 2009) studied the influence of superfine pulverization on the stability of *Sanguis draconis* content in the fine powder ($p < 0.05$) (Zhao et al., 2010).

**Materials and methods**

**Materials**

*Sanguis draconis* was bought from China National Corp. of Traditional and Herbal Medicine (Beijing, China) and was kept in a cool dry room. Seven other medicinal materials were purchased at a local drugstore (Nanchang, China). All medicinal materials were identified by Professor Shouwen Zhang, at JiangXi University of Traditional Chinese Medicine, and the medicinal materials met all requirements from “identification” in 2010 Pharmacopoeia of the People’s Republic of China. The voucher specimens of these eight plants of *Sanguis draconis* (Nº 063416), olibanum (Nº 085127), myrrh (Nº 085128), *Flos Carthami* (Nº 105412), catechu (No. 050233), and cinnabar (Nº 078425) were deposited in the Herbarium of the Department of Pharmacognosy, JiangXi University of Traditional Chinese Medicine. Reference substance, dracorhodin perchlorate, was obtained from the National Institute for the Control of Pharmaceuticals and Biological Products (Nanchang, China).

Male Sprague-Dawley rats were bred at the central animal facility of JiangXi University of TCM (Nanchang, China) and was used. The animals were housed under standard conditions with free access to food and water. All the animal studies were done in accordance with the approved protocols and guidelines of the Institutional Animal Ethical Care Committee (Sharma et al., 2005) and were approved by the local ethics committee for animal experimentation (No. 49101595-1-10). All efforts were made to minimize the number of animals used and their suffering.

**Preparation of fine Qili powder (FP)**

Cinnabar was grounded to a very fine powder (part I). *Sanguis draconis*, olibanum, myrrh, *Flos Carthami* and catechu were subjected to coarse grinding using a 6202 type high speed disintegrator (Huanya-Tianyuan Machine Technology Co., Beijing, China) and screened through a sieve (80 mesh) to separate granulates ($d < 180 \mu m$) (part II). Musk and *Borneolum syntheticum* were triturated into a fine powder (part III). These three parts were sifted and mixed thoroughly.

**Preparation of superfine Qili powder (SP)**

The powders part I, part II and part III were put into the close delivery kettle of a SYFM-8 H II type vibrating ultrafine pulverizer (Powder Technology Engineering Co., Ltd, Jinan,
China), and processed. The temperature was kept at below 5°C to prevent musk and Borneolum synthticum of Qili Powder from volatilizing.

**Determination of powder size**

The average particle size of the FP and SP was determined by dry laser diffraction. Mastersizer 2000 (Malvern instruments Ltd., UK) which equipped with Scirocco dry module was applied in the test. The intake air pressure and feed-rate of operating parameters of the experiment are 2.5 bars and 55%, respectively.

**Specific surface area and pore volume**

The specific surface area and pore volume of the FP and SP were determined by nitrogen gas absorption based on the BET method (Sousa et al., 2002) using TriStar3000 surface area and pore volume analyzer (Micromeritics Instrument Corp., USA).

**Morphology analysis**

The morphology of the FP and SP was evaluated using a MD50 polarizing microscope (Ming-Mei Technology Co., Ltd, Guangzhou, China).

**Bulk density and the angle of repose**

The bulk density and angle of repose were determined using appropriate methods validated previously, by Taser et al. (2005) and Bai et al. (2006), respectively.

**Moisture absorption**

According to the guiding principle of moisture absorption medicine testing of the Pharmacopoeia of the People’s Republic of China (Chinese Pharmacopoeia Commission, 2010) to determine the moisture absorption of the FP and SP.

**Fourier Transform Infrared Spectroscopy (FTIR) and X-ray Diffraction (XRD)**

FTIR spectra of the FP and SP from 400 to 4000 cm⁻¹ were collected by a Vertex70 FTIR (Bruker spectrometer company, Germany). The FP and SP XRD was performed using a D8 ADVANCE X-ray diffraction (Beuker-axs, Germany), with Cu Kr radiation, voltage 40 kV, current 40mA and scanning range of 2θ is 5-50°.

**Content of dracorhodin**

The content of dracorhodin (1) in the FP and SP was determined by HPLC analysis (Wang et al., 2013).

**Dissolution testing**

The dissolution of the FP and SP was tested using Pharmacopoeia of the People’s Republic of China (Chinese Pharmacopoeia Commission, 2010) type 2 dissolution testing apparatus (paddle method). ZRS-8G Intelligent Dissolution Tester (Tianda Tianfa Technology Co., Ltd., China) was used in this study. The weights of the FP and SP were accurately weighed (about 1 g) and put into the vessels with 250 ml double distilled water (n = 6); paddle speed was 100 g and temperature was 37 ± 0.5°C. Samples were taken at 5, 10, 15, 30, 45, 60, 90, 120 min, and replaced with an equal volume of the same fresh medium. An aliquot of 1.5 ml was filtered through a 0.22 μm filter, and the concentration of dracorhodin was determined according to the above-mentioned chromatogram condition.

**Pharmacokinetics**

**LC and MS/MS parameters**

The quantitative analysis was performed on a 6410 Triple Quad LC-MS/MS coupled with an Agilent 1200 HPLC system (Agilent, USA). The chromatography was performed using a Kromosil C18 column (150 x 4.6 mm, 5 μm). The mobile phase consisted of acetonitrile and 0.1% formic acid in double distilled water (55:45 in volume). The flow rate of the mobile phase was set at 0.4 ml/min, the column temperature was 35°C, and the injection volume was 20 μl.

The mass spectrometer was operated at ESI positive ion mode and detection was performed in the multiple reaction monitoring (MRM) modes. The analytes were first characterized by Q1 MS (Q1) scan and enhanced product ion (EPI) scan to determine the precursor ions and product ions used in MRM mode. The MS/MS transitions were: m/z [M+H]+ 267.2 precursor ion to the m/z 252 product ion. The ion spray voltage was set at 3,500 V; ionization temperature was set at 350°C.

**Oral administration**

FP/SP suspension was administered orally at a dose of 12.15 g/kg to rats. Blood samples of about 0.5 ml were collected in heparinized test tubes via the postorbital venous plexus at 0.08, 0.17, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 h after administration. Blood was separated by centrifugation at 4000×g for 10 min, the supernatant was collected and stored at -20°C until analysis.

**Preparation of the plasma sample**

Plasma samples (50 μl) were transferred to centrifuge tubes. 400 μl 6% perchloric acid in water and 400 μl methanol were added to the plasma. The mixture was mixed on a vortex for 2 min, and then centrifuged at 8000×g for 15 min to precipitate protein. The supernatant was transferred to another tube, and the methanol was eliminated by evaporation at 40°C under a gentle stream of nitrogen. The residue I was extracted twice with 400 μl chloroform. The chloroform layer of the residue I was added to the plasma. The mixture was mixed on a vortex for 2 min, and then centrifuged at 8000×g for 15 min to precipitate protein. The supernatant was transferred to another tube, and the methanol was eliminated by evaporation at 40°C under a gentle stream of nitrogen. The residue II was dissolved in 200 μl of 50% methanol solution and vortex-mixed for 2 min. The tubes were centrifuged at 18000×g for 10 min. The supernatants were transferred to vial inserts and 20 μl was injected into LC-MS/MS.

**Calibration curve**

The stock solution was diluted to give solutions of 0.01, 0.50, 1.00, 2.51, 3.51 and 5.01 μg/ml; respectively. Each concentration
was injected in triplicate and the mean peak area was used for the calibration plot.

**Precision**
Dracorhodin (1) standard plasma solution (2.51 μg/ml) was sampled for LC-MS analysis. The work was repeated five times, and to calculate the accurate relative standard deviation (RSD %).

**Repeatability**
Five 2.51 μg/ml dracorhodin standard plasma solutions were sampled for LC-MS analysis, to explore the repeatability of the analysis method.

**Stabilization**
The FP plasma solution after oral administration was sampled for LC-MS analysis respectively after being prepared for 0, 4, 8, 12, and 24 h to ensure stabilization of the solution. The concentration of dracorhodin was obtained by to the above-mentioned chromatogram conditions.

**Statistical analysis**
All pharmacokinetic parameters were calculated using DAS software (Ver. 2.0, Mathematical Pharmacology Professional Committee of China).

**Results and discussion**

**Powder size distribution**
The particle size distribution of the FP and SP can be seen in Fig. 1. The average particle size, $D_{90}$ and $D_{50}$ of the FP were 60.7 μm, 164.5 μm and 28.9 μm, respectively. The average particle size, $D_{90}$ and $D_{50}$ of the SP were 30.1 μm, 32.2 μm and 5.2 μm, respectively.

---

**Specific surface area and pore volume**
The specific surface area (SSA) and pore volume of SP were significantly different ($p < 0.05$) compared with FP. The SP was found to have higher SSA and larger pore volume. Conversely, the FP had lower SSA and smaller pore volume (Table 1). Since higher SSA and pore volume may increase contact area with dissolution medium, they will have effect indirectly on drug dissolution from solid dosage forms (Riley et al., 2008).

**Morphology analysis**
The optical characteristics of Qili Powder are shown in Fig. 2. The eyepiece lens had a magnification of 20× and the objective lens was 40×. The magnification of polarizing microscope was 800 times. In the FP, yellowish-brown long tubular secretory cell of Flos Carthami (a), ellipsoidal pollen grains of Flos Carthami (b), irregular sanguineous pieces around with bright yellow liquid of Sanguis draconis (c), irregular minute granules dark brownish-red lustrous and with dark black edges of cinnabar (d) were clearly observed. For SP (e), the cell walls were broken into pieces and optical microstructure characteristics of Sanguis draconis and cinnabar were disappeared.

**Bulk density and the angle of repose**
The bulk density ($\rho_b$) was the density including pores and interparticle voids. The $\rho_b$ of the FP and SP were 0.3604 and

---

**Table 1**
Specific surface area and Pore volume of fine Qili powder (FP) and superfine Qili powder (SP).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Specific surface area ($m^2/g$)</th>
<th>Pore volume ($cm^3/g$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP</td>
<td>0.2998 ± 0.0051</td>
<td>0.000849 ± 0.000030</td>
</tr>
<tr>
<td>SP</td>
<td>2.0309 ± 0.0471*</td>
<td>0.007062 ± 0.000056*</td>
</tr>
</tbody>
</table>

Mean ± S.D., $n = 3$; *$p < 0.05$ compared to FP.

---

**Figure 1** – Particle size distribution of fine Qili powder (a) and superfine Qili powder (b).

**Figure 2** – Optical microstructure of long tubular secretory cell of Flos Carthami in fine Qili powder (a), pollen grains of Flos Carthami in fine Qili powder (b), pieces of Sanguis draconis in fine Qili powder (c), granules of cinnabar in fine Qili powder (d), superfine Qili powder (e).
0.3732 g/ml, respectively. The \( \rho_b \) varied significantly between the FP and SP \((p < 0.05)\). This might be due to the fact that particle size decreases leading to bulk density increase.

The angle of repose (\( \theta \)) could reflect the change in the fluidity of the powders (Ileleji et al., 2008). The \( \theta \) of FP and SP was 54.64° and 56.85°*, respectively (Table 2). The results confirmed that superfine-treatment had a significant effect on \( \theta \) \((p < 0.001)\). As \( \theta \) increased, the fluidity of powder bulk could diminish.

With the decreasing of particle size, the \( \theta \) of Qili Powder significantly increased \((p < 0.001)\). This result is not in agreement with what the reports stated (Santomaso et al., 2003; Zhao et al., 2009; 2010). The reason might be due to the fact that Sanguis draconis is the main component of Qili Powder, and is a cohesive medicinal material. Sanguis draconis in SP might have been exposed after superfine pulverization, which may be cause of the surface attachment of the SP was higher than that of FP, so the \( \theta \) of SP significantly increased and the fluidity diminished.

**Moisture absorption**

As shown in Figure 3, the powders with different particle size displayed a different curve of moisture absorption. The percentage of moisture absorption of FP and SP slowly increased before 36 h, and reached to balance after 36 h. It was interesting to note that both percentage of moisture absorption and balanced moisture content (BMC) decreased with the decrease of particle size and the increase of SSA. The reason might be related to the cohesive characteristic of Sanguis draconis, a main component in Qili Powder. Sanguis draconis of SP might have been exposed after superfine-treatment. A compact film had formed on the surface of SP after moisture absorption, which blocked up diffusion path of moisture that finally led to a decreased percentage of moisture absorption and BMC.

**FTIR and XRD analysis**

The FTIR spectra and XRD patterns of Qili Powder are shown in Figure 4. From Figure 4A we can see that no molecular structure change occurred between the SP and FP, because the characteristic peaks didn’t show any shifts. There were no differences between the characteristic diffraction peaks of FP and that of SP in Figure 4B, because the old characteristic peaks didn’t disappear and the new characteristic peaks didn’t appear. It meant that superfine pulverization didn’t change the molecular structure and crystal form of Qili Powder.

**Content of dracorhodin**

The identification and quantification of the active ingredient are very important for quality control and efficacy of Qili Powder. The HPLC analysis showed that the dracorhodin \((1)\) did not cause alterations in the chromatographic profile in relation to superfine pulverization (Fig. 5). The contents of dracorhodin in the FP and SP were 1.12 ± 0.02 mg/g and 1.13 ± 0.01 mg/g, respectively. There was no significant difference in dracorhodin content between FP and SP. It means that superfine pulverizing didn’t influence the content of dracorhodin in Qili Powder.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Bulk density (g/ml) Mean ± S.D., ( n = 3 )</th>
<th>Angle of repose (°) Mean ± S.D., ( n = 3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP</td>
<td>0.3604 ± 0.0160</td>
<td>54.64 ± 0.60</td>
</tr>
<tr>
<td>SP</td>
<td>0.3732 ± 0.0133*</td>
<td>56.85 ± 0.36***</td>
</tr>
</tbody>
</table>

*\( p < 0.05 \) compared to FP; ***\( p < 0.001 \) compared to FP.

**Table 2**

**Figure 3** – Curve diagram of moisture absorption of fine Qili powder (FP) and superfine Qili powder (SP).

**Figure 4** – FTIR spectra (A) and XRD patterns (B) of fine Qili powder (a) and superfine Qili powder (b).

**Figure 5** – HPLC chromatogram of dracorhodin \((1)\), fine Qili powder (FP) and superfine Qili powder (SP).
Dissolution testing

The percentage of dissolution of dracorhodin in the FP and SP was studied and the results are shown in Fig. 6. The results showed that lower percentage of dracorhodin dissolution in both FP and SP. This was due to the characteristic liposoluble nature of dracorhodin. However, it was clear that the percentage of dissolution of dracorhodin significantly increased with the decrease of particle size (p < 0.05). There was no difference in the content of dracorhodin between FP and SP therefore, the main factor affecting the dissolution of dracorhodin was proven to be the particle size and the SSA of Qili Powder.

Pharmacokinetics

The calibration plots were linear in the range of 0.01-5.01 μg/ml. The mean of six different calibration plots yielded the equation Y = 34633X + 0.9909. The precision and repeatability of dracorhodin (1) standard plasma solution were 4.5 and 4.8%, respectively. These results showed that the precision and repeatability were favorable. The RSD of stabilization of FP plasma solutions after oral administration was 1.59%, which showed that the solution was stable in 24 h.

The mean plasma dracorhodin concentration–time curve after oral administration of the FP and SP was shown in Figure 7. All pharmacokinetic parameters were calculated by DAS software. The major pharmacokinetic parameters were presented in Table 3. After superfine pulverization, the maximal plasma concentration (C_{\text{max}}) of dracorhodin increased from 0.28 mg/ml to 3.06 mg/ml, while the peak time (T_{\text{max}}) decreased from 11.95 h to 2.10 h. This showed that the SP was absorbed faster than that of FP. The mean residence time (MRT) and the total body clearance rate (CLz/F) of dracorhodin of SP were 31.09 ± 6.14 h and 0.47 ± 0.14 l/h/kg, respectively, which was significantly different from FP (p < 0.05, **p < 0.01). This indicated that the duration of drug effect has been prolonged after superfine pulverization. Therefore, the AUC(0-t) of dracorhodin in SP was 26.84 ± 7.77 mg/l'h, which was 3.75 times of the FP’s (**p < 0.01). This showed that the absorption capacity of the medicine in rats was increased by superfine pulverization. The reason might be due to that the effective contact area of the medicine with the body fluid is increased when the medicine is pulverized to superfine powder. The results of the pharmacokinetics analysis showed that superfine powder has the advantage of faster absorption and higher bioavailability.

Table 3
Pharmacokinetic Parameters of dracorhodin (1) after oral administration of fine Qili powder (FP) and superfine Qili powder (SP)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FP</th>
<th>SP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-0)(mg/l'h)</td>
<td>7.15 ± 1.53</td>
<td>26.84 ± 7.77**</td>
</tr>
<tr>
<td>AUC(0-∞)(mg/l'h)</td>
<td>7.26 ± 1.51</td>
<td>27.42 ± 7.76**</td>
</tr>
<tr>
<td>MRT(0-0)(h)</td>
<td>22.25 ± 2.72</td>
<td>29.75 ± 5.67*</td>
</tr>
<tr>
<td>MRT(0-∞)(h)</td>
<td>23.37 ± 2.39</td>
<td>31.09 ± 6.14*</td>
</tr>
<tr>
<td>t1/2z(h)</td>
<td>10.69 ± 3.56</td>
<td>9.39 ± 4.36</td>
</tr>
<tr>
<td>CLz(F)(l/h/kg)</td>
<td>1.75 ± 0.46</td>
<td>0.47 ± 0.14**</td>
</tr>
<tr>
<td>C_{\text{max}}(mg/l)</td>
<td>0.28 ± 0.06</td>
<td>3.06 ± 1.50*</td>
</tr>
<tr>
<td>T_{\text{max}}(h)</td>
<td>11.95 ± 11.31</td>
<td>2.10 ± 3.31*</td>
</tr>
<tr>
<td>F(%)</td>
<td>100</td>
<td>375.38</td>
</tr>
</tbody>
</table>

Mean ± S.D., n = 6; *p < 0.05 compared to FP; **p < 0.01 compared to FP.

Conclusions

SSA and the pore volume of Qili Powder after superfine pulverization increased. The fluidity of powders decreased with the decreasing of particle size. The percentage of moisture absorption and the balanced moisture content of SP decreased, which may result in a slow agglomeration of SP that finally leads to increased storage stability and prolonged period of guaranteed quality of Qili Powder. Compared with FP the superfine pulverization did not influence the content of dracorhodin nor the molecular structure and crystal form of Qili Powder, but significantly improved the percentage of dissolution and absorption of dracorhodin in rats. The superfine pulverization of Qili Powder showed some physicochemical and medicinal properties that might be of potential use in the drug industry.

According to related works, the general view is that after superfine pulverization SSA of superfine powder increases, which results in easy moisture absorption. With the increase of water content, the stability of TCM preparation decreases, such as charging of chemical component, midewing and so on, and guaranteed quality period was shortened. However,
after superfine pulverization, the rate of moisture absorption and BMC of SP decreased. These results showed that maybe superfine pulverization could increase storage stability of Qili Powder and prolong guaranteed quality period of Qili Powder.

Our results suggested that fluidity was negatively related to the particle size of Qili Powder. The research group has studied Flos Carthami, Angelicae sinensis radix, Radix et rhizoma Notoginseng, Drynariae rhizoma, Radix et rhizoma Rhei, catechu, Sanguis draconis separately and got the same result. Bad fluidity was not conducive to subsequent processing of superfine powders, and may lead to a bigger load difference during the packing process of superfine powders.

To improve bioavailability of SP, the efficacy of superfine powders will be enhanced, which means that dosage can be reduced as well as the raw material, thus minimizing TCM materials, especially the tense situation of endangered TCM biological materials such as musk.

The Pharmacopoeia of the People’s Republic of China (2010 Edition) contains about 1036 kinds of TCM preparations. Among them, 742 kinds are used directly as a medicine in powder form after pulverization, which are about 72% of TCM preparations. It is clear now that a TCM powder is an important intermediate product or end product of TCM preparation. The physicochemical and medicinal properties of a TCM powder is directly related to the particle size of powders. Thus, the physicochemical and medicinal properties of TCM preparations may improve by making TCM powders into superfine powders. Therefore, this study will not only helpful to the application of superfine pulverization in Qili Powder, but also provide a possible method to prepare other TCM powders.

Authors’ contributions

GZ contributed in collecting materials, preparation of powder, and analysis of the data and drafted the paper. CW contributed in preparation of powder and physicochemical studies. XL contributed to pharmacokinetics studies and critical reading of the manuscript. ZL contributed in the identification of biological materials and running the laboratory work. ZX and ZL contributed to chromatographic analysis and critical reading of the manuscript. All the authors have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES


