Regular Article

Self-microemulsifying Drug Delivery System Improved Oral Bioavailability of 20(S)-Protopanaxadiol: From Preparation to Evaluation

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20(S)-Protopanaxadiol (20(S)-PPD) is one type of sapogenin of protopanaxadiols and has a variety of pharmacological activities. In order to improve the dissolution of 20(S)-PPD as well as its oral bioavailability, a self-microemulsifying drug delivery system (SMEDDS) was utilized for 20(S)-PPD preparation. Following the preparation of the 20(S)-PPD SMEDDS, its dissolution, stability, and intestinal absorption in rats were studied, and the pharmacokinetics and optimal dosage after oral administration were evaluated. The dissolution tendency of the SMEDDS in phosphate buffered saline (PBS), 0.1 M HCl and distilled water was consistent. SMEDDS was stable under a condition of high temperature (40°C), high humidity or with strong light irradiation, or within 6 h in artificial digestive tracts. 20(S)-PPD SMEDDS was well-absorbed in all intestinal segments in rats. When the drug concentration was higher than 200 µg/mL or the perfusion flow was faster than 0.5 mL/min, passive diffusion of drug in the duodenum reached a saturated level. In addition, P-glycoprotein inhibitor did not affect the intestinal absorption of 20(S)-PPD SMEDDS. Pharmacokinetic study showed that T_max in male rats was shortened significantly, while C_max and area under the curve (AUC) were remarkably increased. The relative oral bioavailability of 20(S)-PPD SMEDDS was increased approximately three fold compared with the 20(S)-PPD carboxy methyl cellulose (CMC). 20(S)-PPD SMEDDS (100 mg/mL) was administered by gastric infusion to both mice and rats for 14 d. SMEDDS improved the oral bioavailability of 20(S)-PPD and reduced the necessary drug dosage. 20(S)-PPD SMEDDS could become a promising clinical alternative as an anti-tumor or antidepressant drug.

Key words 20(S)-protopanaxadiol; self-microemulsifying drug delivery system; preparation; bioavailability; intestinal absorption; pharmacokinetics

Panax ginseng is documented to tonify internal organs, benefit the spirit, suppress the fright as well as improve eyesight and intelligence.12 The long term application also facilitates relaxation and increases life span.21 Various chemical components were distinguished in Panax ginseng, including saponins, volatile oil, polysaccharides, amino acid and polypeptide, and microelements, of which ginsenosides are the main active ingredients, including oleanic acid (OA), protopanaxadiol (PPD) and protopanaxatriol type (PPT).32 20(S)-PPD (Fig. 1) is one of aglycones of ginsenosides and has a wide range of pharmacological activities, especially in antitumor and neurological function recovery.4–9 However, the low bioavailability of ginsenosides (% for Rb1, 3.4% for Rb2, 1.9% for Rg1) after oral administration restricts their clinical applications.9,11 Importantly, PPD is the final active component after the absorption of ginsenosides in intestine.12,13

A variety of techniques have been applied to improve the bioavailability of drugs with low dissolution and oral availability.14 The typical approaches include salt formation, pH change, β-cyclodextrin complex, microemulsion etc. Self-microemulsifying drug delivery system (SMEDDS) is one method for the improvement of oral bioavailability. A drug delivery system achieved by chemical rather than mechanical means was widely used to improve the bioavailability.15,16 Some well-known chemical compounds with low bioavailability were improved via SMEDDS.17–19

The poor solubility and oral bioavailability of 20(S)-PPD challenge its clinical application.20 In order to increase the solubility of 20(S)-PPD and improve the oral bioavailability, in this study, SMEDDS of 20(S)-PPD was prepared and evaluations were conducted including intestinal absorption, safe administration dosage and pharmacokinetics in vivo.

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Experimental

Materials 20(S)-PPD was purchased from Shanghai Jingke Chemical Science and Technology Corporation (Shanghai, China). Labrafil® m-8940 (Caprylocapryl Tri-glyceride), Transcutol® P (diethylene glycol monoethyl ether) and Labrasol® (Caprylocaproyl Macroglycolicierides) were obtained from Gattefossé (Lyon, France). Oleic acid was obtained from Shanghai Chemical Reagent Corporation (Shanghai, China). Cremophor RH® 40 (Polyoxyethylenehydrogenated-edcastoril) was donated by BASF (Ludwigshafen, Germany). Flutamide was provided by Jiangsu Tasly Diyi Pharmaceutical Corporation (Jiangsu, China).

Preparation of SMEDDS The preparation of SMEDDS was patented and the materials and reagents included 20(S)-PPD (10.0%), Labrasol® (34.3%), Cremophor RH® 40 (11.4%), Transcutol® P (17.3%), Labrafac Lipophile WL 1349 (4.3%), Oleic Acid (22.7%). These materials were placed in a 100 mL conical flask with plug, and then magnetic stirred for 30 min at 45°C. To ensure complete dissolution in the self-microemulsion formulation, shaking or vortex mixing were applied before stirring to make a fast dispersion. The prepared microemulsion formulation, shaking or vortex mixing were selected under high temperature (40, 60°C), high humidity (RH, ±5%) and strong light irradiation (4500 lx ± 500 lx), respectively. After being placed in these conditions, the samples were unloaded and analyzed at different days (day 0, day 5, day 10). Ten milligram of each sample was dissolved with methanol and then diluted to the requisite concentrations. The solution was filtered with 0.45 µm nylon membrane filters. A 200 µL aliquot of the solution was injected into an HPLC analyzer to detect its content as described above.

Emulsion Stability Study
Zero point twenty five gram of 20(S)-PPD SMEDDS in triangle flasks was added to either 0.1 M HCl, distilled water or phosphate buffered saline (PBS) (pH 6.8), to emulsify and disperse it. Medium was them added in the following amounts: 50, 125, and 250 mL. Aliquots were withdrawn at different intervals (0, 2, 4, 6 h), filtered, and the content was determined in the nine samples.

Intestinal Absorption in vivo
The self-microemulsion was mixed with Krebs–Ringer (K-R) solution. The 20(S)-PPD intestinal perfusion solution was prepared at the concentrations of 100, 200, and 400 µg/mL. Another intestinal perfusion solution with 200 µg/mL 20(S)-PPD SMEDDS and 160 mg/L P-glycoprotein (P-gp) inhibitor, verapamil was prepared.

Wistar rats (140–180 g) were obtained from the Laboratory Animal Center of Shanghai University of Traditional Chinese Medicine. All experiments were approved by the Institutional Animal Care and Use Committee of Shanghai University of Traditional Chinese Medicine.

Intestinal absorption in rats was conducted by referring to the literature.20 Rats were anesthetized by intraperitoneal injection of 20% urethane (1.6 g/kg). The intestinal segments were separated and conducted with intubation. Intestinal perfusion was collected 45, 60, 75, 90, 105, and 120 min after drug treatment. Finally, the segments were prepared for the measurements of their length and inner diameters. The collected samples were filtered through 0.45 µm polyethel sulfone membrane filters and the subsequent filtrate was taken and assayed using HPLC with a UV detector. Absorption rate constant (Ka) and apparent absorption coefficient (Papp) of the drug were calculated according to the gravimetric method.21,23 HPLC assay comprised of chromatographic system (Agilent 1100, Agilent Corporation, U.S.A.), chromatographic column (Agilent Eclipse XDB-C 18, 5 µm, 4.6 mm × 150 mm, Agilent Science and Technology Corporation, U.S.A.). The mobile phase was acetonitrile–0.2% phosphoric acid aqueous solution (78:22) with a flow rate of 1.0 mL/min and a column temperature of 25°C. The detection was completed with a UV detector. Theoretical plate numbers should be higher than 10000 when 20(S)-PPD peaks were calculated. K-R solution and vacant self-microemulsion did not influence the determination of intestinal circulation samples.

Appropriate amount of 20(S)-PPD SMEDDS was taken to prepare the 200 µg/mL intestinal perfusion solution with K-R buffer. Rats were treated with the same method as above, and absorption in duodenum, jejunum, ileum and colon were evaluated at the perfusion rate of 0.2 mL/min. The absorption in duodenum was evaluated with different drug concentrations (100, 200, and 400 µg/mL) at the perfusion rate of 0.2 mL/min, and at different perfusion rate (0.2, 0.5, and 0.8 mL/min). In addition, 160 mg/L P-gp inhibitor, verapamil intestinal perfusion solution was prepared by 200 µg/mL drug solution. Rats were treated with the same method as above, and absorption in duodenum was investigated at a perfusion speed of 0.2 mL/min.

Pharmacokinetic Study
20 Wistar rats (10 male and 10 female) weighing 140–180 g were divided randomly into two groups: 20(S)-PPD SMEDDS group (100 mg/kg, oral administration once) and 20(S)-PPD with 0.5% carboxymethyl cellulose (CMC) group (100 mg/kg,
oral administration once).

Blood samples (0.2 mL) were collected from jugular vein at 8, 15, and 30 min, and 1, 2, 4, 6, 8, 12, 24 and 36 h after administration, respectively. The blood samples were placed on ice and plasma samples were separated by centrifugation (8000 rpm × 6 min, 4°C) within 30 min, and then stored at −80°C for use. Fifty microliters of plasma samples were added to 250 µL internal standard solution (ISTD, 25 ng/mL flutamide) and centrifuged (15000 rpm) for 5 min after vortexing for 1 min. A hundred microliters of supernatant was taken for LC/MS/MS analysis. The equipment for analysis included HPLC system (Agilent 1100, Agilent Corporation, U.S.A.), mass spectrometry system (API 4000, Applied Biosystems, U.S.A.) and Phenyl chromatography column (Gemini C6-phenyl, 5 μm, 50×4.6 mm, Guangzhou FLM Scientific Instrument Corporation, China). Mobile phase was water–acetonitrile (20:80) at a flow rate of 0.40 mL·min⁻¹, and column temperature was set at room temperature. As to mass spectrum, ion sources were Turbo spray, spray gas: 60 psi, CUR: 20 psi, CAD: 12, ion source voltage (IS): −5500 V, and ion source temperature (TEM): 550°C. Data of electric potential value were 0.155 ± 0.015 and −12.3 ± 2.1 mV, which ensured the quality of the self-microemulsion system, according to the previous report. 24) In our previous publication,25) we demonstrated that 20(S)-PPD was well absorbed generally in the intestinal tract with the small intestine as its main absorption segment. The general absorption of 20(S)-PPD in the intestine implied that SMEDDS would be an efficient method to promote the bioavailability of 20(S)-PPD.

**Results and Discussion**

**SMEDDS Preparation and Globule Size Analysis**

Smaller globule size is highly preferred, as it provides larger surface area for drug absorption. High ζ potential (negative or positive) indicates greater electrostatic repulsive forces between the globules which prevents the coalescence of Nano emulsion. The negative value indicates that oil globules are negatively charged which may due to the presence of surfactants and/or co-surfactants. 24) With reference to the established quantification, the average drug loading capacity was 95.9 ± 3.97 mg/mL. The globule size of 20(S)-PPD SMEDDS was 57.59 ± 5.44 nm. The polydispersity index (PDI) and electric potential value were 0.155 ± 0.015 and −12.3 ± 2.1 mV, which ensured the quality of the self-microemulsion system, according to the previous report. 24) In our previous publication, 25) we demonstrated that 20(S)-PPD was well absorbed in the intestine implying that SMEDDS would be an efficient method to promote the bioavailability of 20(S)-PPD.

**Dissolution**

The dissolution tendency of the SMEDDS in PBS, 0.1 M HCl and distilled water was consistent. With the increase of medium pH, the average cumulative dissolution rate was decreased (Fig. 2). The dissolution rate in 0.1 M HCl and distilled water within 5 min was around 80–90%, and remained at the high level for at least 60 min. However, the SMEDDS in PBS could dissolve about 60% within 30 min, and hardly be improved within 60 min. The results also showed that the dissolution extent and rate of the SMEDDS appeared to the maximum in the condition of 0.1 M HCl, which is similar to the gastric environment.

**Stability**

The level of 20(S)-PPD SMEDDS remained more than 90% at day 10 in a condition of 40°C, RH92.5% or
with 4500lx irradiation. While the temperature was increased to 60°C, the level was reduced to 86.67%. These data suggest that the SMEDDS is stable under a condition of high temperature (40°C), high humidity or with strong light irradiation. However, the SMEDDS should be stored below a temperature of 60°C.

Emulsion Stability Study The results showed no apparent change in the content of the SMEDDS within 6 h after emulsified with different degrees of dilution. The concentrations of PPD in the 50 mL emulsified solutions were 420.56±5.45 µg/mL (diluted with water), 423.21±8.23 µg/mL (diluted with 0.1 M HCl), and 406.23±4.37 µg/mL (diluted with PBS). When diluted in 125 mL water, HCl and PBS, the concentrations were 175.48±1.60 µg/mL, 155.88±3.99 µg/mL, and 172.25±3.80 µg/mL, respectively. When diluted in 250 mL of each solvent, the emulsified samples contained PPD at concentrations of 87.98±1.49 µg/mL, 62.72±1.37 µg/mL, and 80.27±2.17 µg/mL, respectively. These data suggest that 20(S)-PPD SMEDDS is stable up to 6 h in artificial digestive tracts.

Absorption Parameters of 20(S)-PPD SMEDDS in Rats’ Intestine There was no significant difference regarding the absorption rate constant (K_a) value of 20(S)-PPD SMEDDS among duodenum, jejunum, ileum and colon (p>0.05) (Table 1). By contrast, the apparent absorption constant (P_app) values of each intestinal region were significant different (p<0.05). The P_app value in the ileum segment was much lower than those of the other regions, which indicates that the main absorption sites of 20(S)-PPD SMEDDS are the duodenum, jejunum and colon segments. It was estimated that this difference in the P_app value in the different segments of intestine mainly attribute to the biochemical barrier function of small intestine using in situ perfusion. It was reported that membrane transporters and metabolizing enzymes were shown to affect both rate and extent of intestinal drug absorption. For some compounds, a complex interplay may exist between transporters and metabolizing enzymes upon intestinal transport, which had been observed for dual substrates of CYP3A enzymes and P-gp.26

Effects of Different Drug Concentrations of 20(S)-PPD SMEDDS on Intestinal Absorption Parameters There were significant differences regarding K_a and P_app values at drug concentrations of 100 μg/mL and 200 μg/mL (p<0.05). However, increasing drug concentration to 400 μg/mL did not further affect the P_app and K_a values in the duodenum, indicating saturation was attained (Table 2). Moreover, early studies about pharmaceutical capsules found that the amount of drug for each oral administration was 50 mg.27 Assuming a human’s gastrointestinal fluid is 250 mL, it could be estimated that the concentration of 20(S)-PPD SMEDDS was 200 µg/mL in the intestinal fluids, when the drug dosage in the intestine was 50 mg. Therefore, 200 µg/mL was selected to be the concentration of perfusion fluids.

Effects of Perfusion Flow Speed of 20(S)-PPD SMEDDS on Duodenum Absorption Parameters We detected the effect of perfusion flow speed on the absorption parameters. A perfusion rate ranging from 0.2 to 0.8 mL/min was screened. The results showed that at the drug concentration of 200 µg/mL, the K_a values of 20(S)-PPD SMEDDS at different speeds were not statistically significant (p>0.05), however, the P_app values were statistically significant (p<0.05). These data explained that with the increase of the perfusion rate from 0.2 to 0.5 mL/min, the drug showed a significant increased trend of intestinal absorption P_app (Table 3).

Effects of P-gp Inhibitor on Absorption Parameters Furthermore, the influences of P-glycoprotein inhibitor, verapamil, on the intestinal absorption of 20(S)-PPD SMEDDS were studied. There was no significant difference regarding K_a and P_app values between inhibitor group and the drug group (p>0.05) (Table 4), which indicated that the P-gp inhibitor did not influence the intestinal absorption of drugs. These data suggest that 20(S)-PPD was not a substrate of P-gp.

Pharmacokinetics of Rats after Intragastric Administration with 20(S)-PPD SMEDDS The result of analysis of the specificity of plasma sample in vivo showed that the blank plasma did not affect the measure of 20(S)-PPD and ISTD flutamide under the chromatographic conditions (data were not shown). The standard curve for 20(S)-PPD SMEDDS was established:

\[ Y = 0.00138x + 0.000865, \quad r^2 = 1.0000, \text{ linear range of } 5 - 2500 \text{ ng/mL} \]

The method was reliable due to the good recovery (Table 5). The plasma concentration of the drug peak time (T_{max}) was significantly shortened and peak concentration (C_{max})

Table 1. Absorption Parameters of 20(S)-PPD SMEDDS in Different Regions of Intestine (n=5)

<table>
<thead>
<tr>
<th>Location</th>
<th>K_a×10^{-3} min^{-1}</th>
<th>P_app×10^{-3} cm·min^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>99.05±0.12</td>
<td>9.94±0.77</td>
</tr>
<tr>
<td>Jejunum</td>
<td>99.47±0.23</td>
<td>8.97±0.33</td>
</tr>
<tr>
<td>Ileum</td>
<td>99.30±0.26</td>
<td>5.17±0.21</td>
</tr>
<tr>
<td>Colon</td>
<td>99.24±0.29</td>
<td>10.0±0.59</td>
</tr>
</tbody>
</table>

Table 2. Effects of Different Drug Concentrations of 20(S)-PPD SMEDDS on Intestinal Absorption Parameters (n=5)

<table>
<thead>
<tr>
<th>Drug concentration (µg·mL^{-1})</th>
<th>K_a×10^{-3} min^{-1}</th>
<th>P_app×10^{-3} cm·min^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>97.20±1.22</td>
<td>5.85±0.23</td>
</tr>
<tr>
<td>200</td>
<td>99.05±0.12</td>
<td>9.94±0.77</td>
</tr>
<tr>
<td>400</td>
<td>99.31±0.10</td>
<td>10.02±0.55</td>
</tr>
</tbody>
</table>

Table 3. Effects of Perfusion Flow Rate of 20(S)-PPD SMEDDS on Duodenum Absorption Parameters (n=5)

<table>
<thead>
<tr>
<th>Perfusion rate (mL·min^{-1})</th>
<th>K_a×10^{-3} min^{-1}</th>
<th>P_app×10^{-3} cm·min^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>99.05±0.12</td>
<td>9.94±0.77</td>
</tr>
<tr>
<td>0.5</td>
<td>96.41±1.18</td>
<td>24.63±1.31</td>
</tr>
<tr>
<td>0.8</td>
<td>90.12±6.15</td>
<td>22.86±1.23</td>
</tr>
</tbody>
</table>

Table 4. Effects of P-gp Inhibitor on Absorption Parameters of 20(S)-PPD SMEDDS (n=5)

<table>
<thead>
<tr>
<th>Groups</th>
<th>K_a×10^{-3} min^{-1}</th>
<th>P_app×10^{-3} cm·min^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>99.05±0.12</td>
<td>9.94±0.77</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>98.59±0.69</td>
<td>10.86±1.13</td>
</tr>
</tbody>
</table>
was significantly increased after 20(S)-PPD SMEDDS oral application compared with control (Table 6). Elimination half-life ($t_{1/2}$) was significantly prolonged and area under the curve ($AUC_{(0-\infty)}$) was significantly increased (ANOVA, p<0.05). Compared with an equal dose of suspension, the relative bioavailability was increased to a 2.3-fold level. However, the pharmacokinetic properties of 20(S)-PPD SMEDDS in rats showed significant gender difference (ANOVA, p<0.05). The main pharmacokinetic parameters including $t_{1/2}$, $C_{max}$, $AUC_{(0-\infty)}$, $AUC_{(0-\infty)}$ and MRT($0-\infty$) in male Wistar rats were lower than those in female rats. Moreover, $T_{max}$ in male rats was higher than that in female rats. In contrast, with the oral application of 20(S)-PPD suspension, the main pharmacokinetic parameters ($t_{1/2}$, $T_{max}$, $C_{max}$, $AUC_{(0-\infty)}$, $AUC_{(0-\infty)}$ and MRT($0-\infty$)) in male rats were lower than those in female rats. The drug–time curves after applications of 20(S)-PPD SMEDDS and 20(S)-PPD were shown in Fig. 3.

Both of rats and mice were applied to conduct preliminary study of pharmacokinetics. The data determined that the follow-up pharmacokinetics administration dosage was 100 mg/kg.

The pharmacokinetic data of 20(S)-PPD showed that after oral treatment with 20(S)-PPD SMEDDS the relative bioavailability was enhanced approximately three fold compared with the same dosage of suspension. In addition, the drugs have significant gender differences in pharmacokinetic properties, i.e., the pharmacokinetic parameters of male rats were lower than those in female rats, suggesting that the drug in clinical use should consider the patients’ gender. It has been reported\textsuperscript{28} that most antidepressants were more effectively absorbed under basic conditions. Compared with males, females secrete less gastric acid resulting in a more basic environment, which could potentially lead to enhanced absorption of antidepressants in the stomach. In addition, females have a slower rate of gastric emptying than males do, thus increasing antidepressant absorption time. Maybe it can partly explain the gen-

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**Table 5. Results of Recovery Tests of Rat Plasma after Administration**

<table>
<thead>
<tr>
<th>Addition (ng·mL$^{-1}$)</th>
<th>Recovery (%)</th>
<th>Average recovery (%)</th>
<th>RSD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>114.83</td>
<td>99.80</td>
<td>88.12</td>
</tr>
<tr>
<td>400</td>
<td>100.44</td>
<td>114.90</td>
<td>99.96</td>
</tr>
<tr>
<td>2000</td>
<td>101.54</td>
<td>111.95</td>
<td>101.49</td>
</tr>
</tbody>
</table>

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**Table 6. Pharmacokinetic Parameters after Oral Administration of 20(S)-PPD SMEDDS and 20(S)-PPD Suspension ($\bar{x}\pm s$, n=5)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Suspension</th>
<th>SMEDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>1.45±0.14</td>
<td>3.98±0.33</td>
</tr>
<tr>
<td>$T_{max}$ (h)</td>
<td>6.00±0.00</td>
<td>7.20±1.10</td>
</tr>
<tr>
<td>$C_{max}$ (µg·L$^{-1}$)</td>
<td>1234.53±429.38</td>
<td>2544.00±326.18</td>
</tr>
<tr>
<td>$AUC_{(0-\infty)}$ (µg·L$^{-1}$·h$^{-1}$)</td>
<td>5588.50±1278.06</td>
<td>21526.84±5611.76</td>
</tr>
<tr>
<td>$AUC_{(0-\infty)}$ (µg·L$^{-1}$·h$^{-1}$)</td>
<td>5728.70±1273.27</td>
<td>21616.92±5645.94</td>
</tr>
<tr>
<td>MRT($0-\infty$) (h)</td>
<td>6.25±0.35</td>
<td>8.61±0.89</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01 compared with corresponding gender in suspension group. * p<0.05, ** p<0.01 compared with male animal treated with 20(S)-PPD SMEDDS.

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Fig. 3. The Drug–Time Curves after Applications of 20(S)-PPD SMEDDS and 20(S)-PPD Suspension in Male and Female Animals

Plasma concentration–time curve after 20(S)-PPD-SMEDDS (A) average oral administration in male and female (100 mg/kg, n=5). Plasma concentration–time curve after 20(S)-PPD-suspension (B) average oral administration in male and female animals (100 mg/kg, n=5).
nder difference of pharmacokinetic performance of 20(S)-PPD.

**Determination of Safe Administration Dosage** The mice received intragastric administration with $10\text{mL/kg}$, $20\text{mL/kg}$ 20(S)-PPD SMEDDS, which was equivalent to $1.0\text{g/kg}, 2.0\text{g/kg}$ 20(S)-PPD, respectively. Forty milliliters/kilogram 20(S)-PPD suspension was applied as the control, which was equivalent to $12.0\text{g/kg}$ PPD. Fifteen minutes after administration, the activity of the mice decreased. Activity returned to normal levels in 45 min after administration. None of the animals died within the 14-d experimental period. There was no statistical difference in the body weight of the mice after drug applications. The animals were sacrificed 14d after administration and no apparent pathological change was observed.

The safe administration dosages of 20(S)-PPD SMEDDS for rats and mice were $2.0\text{g/kg}$ and $1.0\text{g/kg}$, respectively. The safe administration dosage of 20(S)-PPD suspension for mice was $12.0\text{g/kg}$.

**Conclusion** Through this study, a self-microemulsion delivery system for 20(S)-PPD was prepared. The dissolution tendencies of the SMEDDS in several solutions were consistent. Importantly, SMEDDS is stable under high temperature (40°C), high humidity or with strong light irradiation, and within 6 h in artificial digestive tracts. 20(S)-PPD suspension was applied as the control, which was equivalently absorbed well in the whole intestine. The relative oral bioavailability of 20(S)-PPD SMEDDS was increased approximately three fold when compared with the control group. The formulation may not only increase patient compliance, but may also improve the therapeutic effects and reduce the application dose. Therefore, 20(S)-PPD SMEDDS should be considered for developing into a new type of anti-depressant or anti-tumor drug.

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**Conflict of Interest** Yuqin Wang is an employee of Shanghai BioAsia Life Technology Co., Ltd., and Peiying Wu is an employee of Shanghai Xingling Science and Technology Pharmaceutical Co., Ltd.

**References**