Characterization, biodistribution and targeting evaluation of breviscapine lipid emulsions following intravenous injection in mice

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Abstract
Breviscapine lipid emulsions were prepared by a high speed dispersion-homogenization method with optimal formulation and technological method. The proportion of liposomes in breviscapine lipid emulsions, an important character for determining the behavior of drug in vivo belongs to which carriers, was less than 5%. Loading breviscapine into lipid emulsions did increase the breviscapine concentrations in plasma, retarded the clearance, and exhibited the properties of sustained-release concluded by pharmacokinetic parameters: after bolus administration, the elimination phase (t_{1/2β} = 99.535) of lipid emulsions was 5.4-times longer than that of Injectio Breviscapine. The AUC_{0→∞} (14.453-times), k_{0} (0.047-times), Cl (0.147-times), and MRT_{P→∞} (17.766-times) values also confirmed this trend. The amount of drug in every tissue increased at different levels after intravenous administration of breviscapine lipid emulsions compared with Injectio Breviscapine. The relative exposure value of breviscapine lipid emulsions for plasma and lungs were 29.59 and 5.81, respectively, indicating that the exposure of breviscapine to plasma and lungs was significantly increased by entrapment in lipid emulsions. Other targeting evaluation indexes also proved the superiority of lipid emulsions carrier to deliver drug to the targeting region of vascular and lung diseases therapy.

Keywords: Breviscapine; lipid emulsions; liposomes contamination; pharmacokinetics; tissue distribution

Introduction
Breviscapine, a flavone glucuronide, is a cardiovascular medicine extracted from a Chinese herb Erigeron breviscapinus (Vant.) Hand.-Mazz. It can promote blood circulation, remove blood stasis, and dredge the meridian passage (Zhu, 1937). Modern pharmacological research shows breviscapine has a therapeutic effect on lung and vascular diseases. Research proved breviscapine was useful in inhibiting pulmonary fibrosis, and could reduce the damage caused by oxygen-derived free radicals in bleomycin (Li, 2009). Scutellarin (4', 5, 6-tetrahydroxyflavone-7-O-glucuronide), the major active component of breviscapine, prevented vascular endothelial dysfunction in diabetic rats (Zhu et al., 2000), and was capable of inhibiting the proliferation of high glucose- and hypoxia-stimulated proliferation of human retinal endothelial cells (HREC), which was possibly related to its ability to suppress the vascular endothelial growth factor (VEGF) expression (Gao et al., 2008). Scutellarin also inhibited platelet aggregation induced by arachidonic acid (AA), adenosine diphosphate (ADP), and platelet-activating factor (PAF) (Chen et al., 2006). Breviscapine and its preparation (Injectio Breviscapine) were listed in the Pharmacon Criteria (Chinese Traditional Patent Medicine).

It was reported that the concentration of breviscapine in plasma declined rapidly after a bolus administration in mice \( t_{1/2(α)} \text{ plasma} = 1.954 \text{ min}, \ t_{1/2(β)} \text{ plasma} = 13.695 \text{ min} \) (Xiong et al., 2009). The result of biodistribution study...
of scutellarin in mice after intravenous injection showed that most of the $^3$H-scutellarin accumulated in the cholecyst, intestine, and dejecta within 1h, and 41.2% of $^3$H-scutellarin was found in the excrement and urine within 24h (Cai, 1981). Lipid emulsions are one of the lipid-based drug delivery systems such as liposomes and solid lipid nanoparticles. The transformation of a free drug into lipid-based drug delivery systems is a strategy to control and modify its pharmacokinetics and tissue distribution (Baldeschweiler, 1990; Dass et al., 2000; Hong et al., 2001; Ji et al., 2006; Tang et al., 2010). In the present research, we studied pharmacokinetics, tissue distribution, and targeting property of breviscapine lipid emulsions. The proportion of liposomes in lipid emulsions was an important factor impacting drug behavior in vivo. We also research the proportion of liposomes with different formulations. This lays down the groundwork for research and development on advanced targeting drug delivery of Traditional Chinese Medicine.

Materials and methods

Materials

Breviscapine was provided by Jiangsu Chia-tai Tianqing Pharmaceutical Co. Ltd (Jiangsu, China). Scutellarin standard (purity > 98%) was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Lipoid E80 (egg yolk lecithin with 80–85% of phosphatidylcholine) was purchased from Lipoid GmbH (D-Ludwigshafen, Germany). Poloxamer 188, 388, 407, and Cremophor EL were purchased from BASF (China) Co., Ltd. (Shanghai, China). Tween 80, Brij 35, and Mrij 59 were purchased from Nanjing Will Chemical Co., Ltd. (Nanjing, China). Calcein were purchased from Shanghai Haoran Bio. Technologies Co., Ltd. (Shanghai, China). Injectable Breviscapine, which is an injection solution of scutellarin (20 mg/5 ml), was produced by Gejiu Bio-Medicine Industry Ltd. (Yunnan, China). Other chemicals used were of analytical grade.

Preparation of breviscapine lipid emulsions

Breviscapine lipid emulsions were prepared as previously described (Xiong et al., 2010). In brief, the emulsions formulation was composed of breviscapine (0.04%), Lipoid E80 (1.2%), $V_e$ (0.06%), oleic acid (1.2%), soybean oil (8.8%), Poloxamer 188 (2.0%), glycerin (2.25%), and double distilled water. The preparation process was shown in Scheme 1.

Characterization of breviscapine lipid emulsions

The mean particle size of the lipid emulsions was determined by photon correlation spectroscopy (MsaterSizer 3000, Malvern Instruments Co., Worcestershire, UK). Data were analyzed in terms of intensity, volume, and number distributions, and reported as $z$-average diameter. The zeta potential was obtained by measuring the electrophoretic mobility (Malvern Zetasizer 3000, Malvern Instruments Co.). Osmotic pressure could influence the stability and particle size of lipid emulsions. It was very important to keep a steady osmotic pressure during the measurement procedure of particle size. Therefore, all samples were diluted 100-times by 2.25% glycerin to keep the steady osmotic pressure.

The concentration of scutellarin in breviscapine lipid emulsions was measured by RP-HPLC with dissolving breviscapine lipid emulsions in 10% Triton X-100 in ethanol for breaking emulsion. A 20 µl aliquot of the supernatant fluid of broken breviscapine lipid emulsions was injected into HPLC for assay. The chromatographic system is presented later.

Determination of acid value and methoxyaniline value

The acid value and methoxyaniline value were determined to evaluate the degradation of lipids in emulsions after sterilization. The acid value and methoxyaniline value were assayed and calculated by titration method.
using phenolphthalein as an indicator of the end-point (Li et al., 2007), and the color reaction of methoxianiline and the aldehydic compounds under acidic conditions affording yellowish products which absorb at wavelengths of 350 nm (Shahidi et al., 2007), respectively.

**Determination of liposomes contamination**

The proportion of liposomes in the emulsions system was determined by the method of Park et al. (1999) using calcine as a water-soluble marker with modifications. The separation condition of calcine and liposomes was established first. Aliquots of 0.5 ml blank liposomes (prepared in the same manner as breviscapine lipid emulsions except no soybean oil was added) and 0.2 mg/ml calcine solution were loaded separately on a Sphadex G-50 gel permeation chromatographic column (1.5 x 50 cm) to determine which flow part should be collected. The column behavior of breviscapine lipid emulsions without soybean oil was just that of liposomes contaminating the lipid emulsions. The flow rate was 1 ml/min. The mobile phase was PBS (pH 7.4) and the volume of each collection was 5 ml per vial. Then each collection was detected at 500 nm for blank liposomes using a UV-VIS collection was 5 ml per vial. Then each collection was ing the lipid emulsions. The flow rate was 1 ml/min. The recovery of phospholipids was also determined with two emission spectra (Hitachi F-4500, Japan). The column oven (Timberline Instruments, Boulder, CO) maintained in a column oven (Shimazu UV3600, Japan) and at Ex/Em = 490 nm/520 nm for calcein using fluorescence NIR spectrophotometer (Shimazu UV3600, Japan) and at Ex/Em = 490 nm/520 nm for calcein using fluorescence emission spectra (Hitachi F-4500, Japan). The column recovery of phospholipids was also determined with two concentrations of 12 mg/ml and 32 mg/ml phospholipids in water loaded on column. Phospholipids were measured colorimetrically by forming a complex with ammonium ferrothiocyanate, as in Stewart (1980).

To investigate the effect of different surfactants on the proportion of liposomes in the emulsions system, emulsions with different water phases were prepared for contrast. The same procedures were applied for preparing contrast emulsions as for breviscapine lipid emulsions except for no or required amount of different surfactants (Poloxamer 338, Poloxamer 407, Tween 80, Cremophor EL, Brij 35, and Mrj 59), and 0.2 mg/ml calcine as a water-soluble marker added to the water phase. A 0.5 ml aliquot of both liposomes and emulsions were then loaded separately on a Sphadex G-50 to separate free calcine from that entrapped inside the liposomes. The flow parts of liposomes were collected and combined. The fluorescence intensity of calcine in a combined sample was determined with dissolving it in 10% Triton X-100 in ethanol. The fluorescence intensity of calcine from each emulsion was compared with the fluorescence intensity of calcine from the pure liposome preparation (Lipoid E80 only). The ratio of fluorescence intensity given by emulsions (as measured by the phospholipids concentration) to that of the pure liposomes (composed of equal amounts of phospholipids of emulsions) was presented as the percentage of liposomal fraction in the emulsions system.

**Biosamples disposal procedure**

Biosamples (including plasma, liver, spleen, lungs, and kidneys) were disposed as previously described (Xiong, 2006b). In brief, a 200 µl aliquot of methanol was added to 100 µl aliquot of plasma and homogenate (10%, w/v) of tissues with 1% sodium bisulfate in each biosample. Then, the mixed samples were shaken on a SW-80A vortex shaker (Shanghai Medical University Instrument Plant, Shanghai, China) and were centrifuged at 10,000 g for 10 min at 4°C (Refrigerated Centrifuge 3K30, Sigma, German). A 20 µl aliquot of the supernatant fluid was injected into HPLC for assay.

**HPLC analysis**

The chromatographic system (Xiong et al., 2006a) consisted of a Waters 510 HPLC pump and a Waters 486 Absorbance UV detector (Waters Corp., Milford, MA). The wavelength of this detector was set to 335 nm. The HPLC system was controlled by a computer employing the Millennium 2010 ChemStation software. The analytical column was a reverse phase Hypersil C₈ column (250 x 4.6 mm, 5 µm particle size; Dalian Elite Analytical Instrument Co., Ltd., Dalian, China) maintained in a column oven (Timberline Instruments, Boulder, CO). The mobile phase was composed of methanol-water-glacial acetic acid (40:60:1). Elution was performed isocratically at 40°C at a flow-rate of 1.0 ml/min.

**Pharmacokinetics and tissue distribution assay**

Kunming mice with an average weight of 20 g were used in this study. The mice were divided into two groups of three-to-five animals. Breviscapine lipid emulsions and Injectable Breviscapine were injected intravenously into the tail vein of the mice (25 mg/kg). Animals were sacrificed under ether anesthesia at indicated intervals after administration. Blood was collected in heparin-coated tubes and centrifuged at 1000 g for 5 min to separate the plasma. Liver, spleen, lungs, and kidneys were removed, weighed, and homogenized (10%, w/v) in a solution of 1% sodium bisulfate in physiological saline. All samples were immediately frozen at ~20°C until analysis. Pharmacokinetic parameters for scutellarin following administration of commercial and lipid emulsions preparations were determined from the concentration-time data. A computer program 3P97 (Administration of Health, Beijing, China) was used for the fitting of pharmacokinetic models.

**Targeting assay**

In order to evaluate biodistribution of breviscapine lipid emulsions in heart and other tissues compared with Injectable Breviscapine, some targeting parameters were analyzed in this study (Ping, 1998). Areas under
the plasma and tissue concentration-time curves (AUC) were calculated by logarithmic trapezoidal method as followed:

\[
\sum_{i=1}^{n} AUC = \frac{(C_{i+1} - C_i)(t_{i+1} - t_i)}{\ln C_{i+1} - \ln C_i}
\]

where \(C_i\) is the concentration of scutellarin in biosample at time point \(t_i\); \(C_{i+1}\) is the concentration of scutellarin in biosample at next time point \(t_{i+1}\).

To express relative exposure (Re) of drug delivery systems, the AUC of lipid emulsions was divided by the AUC of injection in certain tissue. Re was expressed as follows:

\[
Re = \frac{AUC_{lipid\ emulsions}}{AUC_{injection}}
\]

Effect of different surfactants on particle size of breviscapine lipid emulsions was also studied and listed. The results suggest every surfactant could decrease particle size to varying degrees. Oily droplets were smaller with Cremophor EL (180.2 ± 23.6 nm) and Tween 80 (205.7 ± 10.7 nm) adding to the emulsions system. However, Cremophor EL is used in Taxol (paclitaxel) and has been called as a dose-limiting agent because of its serious or life-threatening allergic reaction (Gelderblom et al., 2001; Chao et al., 2005). Also, Tween 80 was reported to have a remarkable hemolytic activity (Alvarez-Núñez et al., 1999). Other surfactants showed no extra advantages in comparison to Poloxamer 188. Therefore, Poloxamer 188 was not only safe (Grindel et al., 2002), but also effective on reducing oily droplets size (219.0 ± 8.3 nm with 2% concentration) of lipid emulsions concluded from these results.

### Results and discussion

#### Preparation and characterization of breviscapine lipid emulsions

The optimal formulation and technological method were used for the preparation of sterile and stable breviscapine lipid emulsions for intravenous administration in the present study. Breviscapine has low aqueous solubility and poor chemical stability. The preparation can protect breviscapine from degradation by adding \(V_e\) in oil phase, increase insoluble drug load in water-based drug delivery system, as well as be produced on large industrial scale and sterilized by autoclaving (Park et al., 1999). The average particle size, zeta potential, and content of final product were 228.1 ± 10.2 nm, −27.9 ± 2.1 mV, and 95.2 ± 0.8% (\(n=3\)), respectively. The acid value and methoxylaniline value were 0.2–0.3 and 0.8–1.4 after sterilization, respectively. \(V_e\) in the oil phase could protect the lipid from degradation to a certain extent. The results meet the requirement of Chinese Pharmacopoeia.

#### Effect of surfactants on particle size of lipid emulsions

Retention of drug in the emulsions after i.v. injection depended on their size (Kurihara et al., 1996). The effect of different surfactants on particle size of breviscapine lipid emulsions was also studied and listed in Table 1. The results suggest every surfactant could decrease particle size to varying degrees. Oily droplets were smaller with Cremophor EL (180.2 ± 23.6 nm) and Tween 80 (205.7 ± 10.7 nm) adding to the emulsions system. However, Cremophor EL is used in Taxol (paclitaxel) and has been called as a dose-limiting agent because of its serious or life-threatening allergic reaction (Gelderblom et al., 2001; Chao et al., 2005). Also, Tween 80 was reported to have a remarkable hemolytic activity (Alvarez-Núñez et al., 1999). Other surfactants showed no extra advantages in comparison to Poloxamer 188. Therefore, Poloxamer 188 was not only safe (Grindel et al., 2002), but also effective on reducing oily droplets size (219.0 ± 8.3 nm with 2% concentration) of lipid emulsions concluded from these results.

### Determination of liposomes contamination

There was a certain amount of liposomes mixed in a lipid-based emulsions system during the preparation procedure (Groves et al., 1985; Wheeler et al., 1994). It was an important character for lipid emulsions because the behavior of lipid emulsions in vivo was different from that of liposomes. Furthermore, drug leakage from liposomes also affect single behavior of drug loaded in carriers in vivo. The proportion of liposomes in breviscapine lipid emulsions system was determined using calcein as a water-soluble marker. The calibration curve for calcein was \(I = 5.58C + 1.219\) and linear in the range of 1–10 ng/ml, where \(I\) and \(C\) were fluorescence intensity and concentration of calcein, respectively. The regression coefficient \(r^2\) was greater than 0.999. Blank liposomes and free calcein were well separated as shown in elution curves of Sephadex G-50 column in Figure 1. No.4 to No.8 vials should be collected and combined in further

#### Table 1. Effect of different surfactants on particle size and proportion of liposomes in lipid emulsions system composed of soybean oil and phospholipids (PL).

<table>
<thead>
<tr>
<th>Composition</th>
<th>Weight ratio</th>
<th>Liposomes contamination (%)</th>
<th>Particlesize(^a) (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil/PL</td>
<td>1:0.32</td>
<td>16.3</td>
<td>246.2 ± 16.5</td>
</tr>
<tr>
<td>Oil/PL/Poloxamer 188</td>
<td>1:0.12:0.2</td>
<td>4.2</td>
<td>219.0 ± 8.3</td>
</tr>
<tr>
<td>Oil/PL/Poloxamer 338</td>
<td>1:0.12:0.3</td>
<td>3.6</td>
<td>236.5 ± 4.6</td>
</tr>
<tr>
<td>Oil/PL/Poloxamer 407</td>
<td>1:0.12:0.2</td>
<td>2.8</td>
<td>255.1 ± 3.3</td>
</tr>
<tr>
<td>Oil/PL/Tween 80</td>
<td>1:0.12:0.2</td>
<td>2.9</td>
<td>220.4 ± 13.9</td>
</tr>
<tr>
<td>Oil/PL/Poloxamer 407</td>
<td>1:0.12:0.2</td>
<td>2.6</td>
<td>227.0 ± 15.5</td>
</tr>
<tr>
<td>Oil/PL/Cremophor EL</td>
<td>1:0.12:0.2</td>
<td>3.1</td>
<td>205.7 ± 10.7</td>
</tr>
<tr>
<td>Oil/PL/Mrij 35</td>
<td>1:0.12:0.2</td>
<td>2.9</td>
<td>180.2 ± 23.6</td>
</tr>
<tr>
<td>Oil/PL/Mrij 59</td>
<td>1:0.12:0.2</td>
<td>2.6</td>
<td>231.6 ± 20.3</td>
</tr>
</tbody>
</table>

\(^a\) The particle size of emulsions was the value of \(Z\)-average diameter using photo correlation spectroscopy (\(n=3\)).
experiments for determination of column recovery of phospholipids and amount of calcein entrapped inside liposomes.

The column recovery of phospholipids was 98.05 ± 0.75% for 12 mg/ml sample and 99.71 ± 1.29% for 32 mg/ml sample (n = 3), respectively. These results suggest that there were almost no phospholipids retaining on column.

The effect of different surfactants on the proportion of liposomes in the lipid emulsions system was summarized in Table 1. Based on the data, liposomes contamination decreased dramatically when surfactants add to the lipid emulsions system. Although Poloxamer 188 did not have the highest ability to reduce the proportion of liposomes, it was the safest surfactant for intravenous preparations. Also, the behavior of liposomes and drug leakage from the part of liposomes in vivo could be neglected when the proportion of liposomes in lipid emulsions system was lower than 5%.

**Pharmacokinetics and tissue distribution assay**

The mean plasma concentration vs time profile of scutellarin following intravenous administration of *Injectio Breviscapine* and breviscapine lipid emulsions is shown in Figure 2. Both curves fit the open two-compartment model by 3P97 program. The pharmacokinetic parameters of two preparations are reported in Table 2. Breviscapine has a short biological half-life (t_{1/2α} = 1.846 min, t_{1/2β} = 18.382 min) and rapid elimination rate (C_l = 3.793 ml/min) from the plasma, and these results were similar to those reported previously [6]. Loading breviscapine into lipid emulsions produced a significant change in pharmacokinetic parameters: after bolus administration, the lipid emulsions were more slowly removed from plasma compared with injection. The elimination phase (t_{1/2β} = 99.535) of lipid emulsions was 5.4-times longer than that of injection. The AUC, k_{ul}, Cl_{p} and MRT values confirmed this trend. Increasing amount and prolonging retention time of drug in plasma with lipid emulsions administration were all beneficial to vascular diseases therapy.

The concentration-time curves of scutellarin in tissues following intravenous administration of *Injectio Breviscapine* and breviscapine lipid emulsions is shown in Figure 3. The AUC value of two preparations was listed in Table 3. The amount of drug in every tissue studied in this paper increased at different levels after intravenous administration of breviscapine lipid emulsions compared with *Injectio Breviscapine*. Under normal circumstances, lipid emulsions injected into the venous system is largely taken up by hepatic and splenic macrophages (Chao et al., 2005). Nevertheless, little increase of drug in liver (compared with spleen) was observed after intravenous administration of breviscapine lipid emulsions. This was possibly because breviscapine was a chemically unstable drug and easily degraded by the liver’s contribution to drug metabolism. Drug-in-lipid emulsions and injection both rapidly degraded and were metabolized in the liver. Therefore, AUC of lipid emulsions in liver (192.35
µg • min/ml) increased slightly vs that of injection (125.06 µg • min/ml). The lungs accumulation of encapsulated drug in breviscapine lipid emulsions may be explained by the physical trapping of emulsions in the vascular network of lungs, taking up the emulsion droplets in lung macrophages and the drug is not bioavailable to the mucosa. Accumulation of drug in lungs with a lipid emulsions carrier may be of benefit for therapy in lung diseases. However, attention should also be paid to the increasing amount of drug in the kidneys to avoid potential safety problems in future research.

**Targeting assay**

Relative exposure plays the most prominent role in evaluation for targeting carriers. If the Re value is greater than 1, the tissue is exposed to drug in the lipid emulsions to a greater extent than that in solution injection. In our study, the Re value of breviscapine lipid emulsions for plasma and lungs were 29.59 and 5.81, respectively, indicating that the exposure of breviscapine to plasma and lungs was significantly increased by entrapment of drug in lipid emulsions.

Although Re provides a good indication about the relative efficacy of two delivery systems for delivery of drug to target tissue, to a given delivery system, it does not provide any information about the drug delivery efficacy to tissue under the premise of equal contribution of drug in plasma to that in tissue. For eliminating the disturbance of drug in plasma, targeting efficacy was introduced in this study. With the contribution of drug in plasma to that in tissue being eliminated, the targeting efficacy of two preparations could be concluded obviously by the ratio of Te in Table 3. The drug distributing to the spleen was most and the drug distributing to the lungs was more than the liver and kidneys.

The Ce also demonstrated the efficiency of a delivery system on the biodistribution. Except for the largest Ce value of the reticuloendothelial system (RES)-rich spleen, Ce value of plasma and lungs were larger (1.52 and 2.28, respectively). On the basis of the above results, it can be concluded that encapsulation of breviscapine into lipid

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**Figure 3.** The concentration-time curves of scutellarin in tissues of mice given *Injectio Breviscapine* (Δ) and breviscapine lipid emulsions (○) after intravenous administration. (a) liver; (b) spleen; (c) lung; (d) kidneys. Each point represents the mean ± SD of three-to-five mice.

**Table 3.** AUC and targeting parameters of *Injectio Breviscapine* and breviscapine lipid emulsions after intravenous administration in mice.

<table>
<thead>
<tr>
<th>Sample matrix</th>
<th>AUC (µg•min/ml or g)</th>
<th>Re</th>
<th>Te</th>
<th>Ratio of Te</th>
<th>Ce</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>59.08</td>
<td>1748.10</td>
<td>29.59</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Liver</td>
<td>125.06</td>
<td>192.35</td>
<td>1.54</td>
<td>2.12</td>
<td>0.11</td>
</tr>
<tr>
<td>Spleen</td>
<td>25.87</td>
<td>919.56</td>
<td>35.55</td>
<td>0.44</td>
<td>0.53</td>
</tr>
<tr>
<td>Lungs</td>
<td>12.94</td>
<td>75.20</td>
<td>5.81</td>
<td>0.22</td>
<td>0.04</td>
</tr>
<tr>
<td>Kidney</td>
<td>11.24</td>
<td>47.94</td>
<td>4.27</td>
<td>0.19</td>
<td>0.03</td>
</tr>
</tbody>
</table>
emulsions could improve the drug distribution in plasma and lungs.

Although the targeting results of plasma and lung were not better than spleen, the drug amount of breviscapine lipid emulsions in plasma and lungs were 29.59- and 5.81-fold higher than that of solution injection under the same administration dosage. The increase was considerable and would induce a better therapeutic effect in vascular and lung diseases.

Conclusion

The proportion of liposomes in breviscapine lipid emulsions was less than 5% with the optimal formulation and technological methods used in this paper. The behavior of drug in vivo could be almost regarded as a function of the lipid emulsions carrier. Based on pharmacokinetics and distribution results, higher promoting blood circulation activity and anti-pulmonary fibrosis effect of lipid emulsions than that of injection may be expected in further studies on pharmacodynamics.

Declaration of interest

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