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Preparation and evaluation of self-microemulsifying drug delivery system of oridonin

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Abstract

The objective of this study was to develop self-microemulsifying drug delivery system (SMEDDS) to enhance the oral bioavailability of the poorly water-soluble drug, oridonin. The influence of the oil, surfactant and co-surfactant types on the drug solubility and their ratios on forming efficient and stable SMEDDS were investigated in detail. The SMEDDS were characterized by morphological observation, droplet size and zeta-potential determination, cloud point measurement and *in vitro* release study. The optimum formulation consisted of 30% mixture of Maisine 35-1 and Labrafac CC (1:1), 46.7% Cremopher EL, and 23.3% Transcutol P. *In vitro* release test showed a complete release of oridonin from SMEDDS in an approximately 12 h. The absorption of oridonin from SMEDDS showed a 2.2-fold increase in relative bioavailability compared with that of the suspension. Our studies demonstrated the promising use of SMEDDS for the delivery of oridonin by the oral route.

Keywords: Self-microemulsifying drug delivery system; Oridonin; Bioavailability

1. Introduction

Oridonin (Fig. 1.), an *ent*-kaurane diterpenoid compound ($C_{20}H_{28}O_6$), is isolated from the Chinese herb *Raddosia rubescens* (*Hamsl.*) *Hara*. Oridonin has shown various pharmacological and physiological effects such as anti-tumor, anti-bacteria, scavenging active oxygen free radicals, and anti-inflammatory properties (Fuji et al., 1989; Osawa et al., 1994; Zhang et al., 1999). The remarkable effect on treating human cancers especially esophageal and hepatic carcinoma has drawn great attention during the last 30 years (Zhang and Ren, 2003). Mechanisms of oridonin action include: inhibiting cell growth in many cancer cells; inducing cell apoptosis; inhibiting DNA, RNA and protein synthesis (Ikezoe et al., 2003; Leung et al., 2005; Li and Zhang, 1988; Liu et al., 2004). All of the commercially available tablets are crude extracts with low oridonin content leading to correspondingly low therapeutic effect and requiring a large dose (6–15 tablets per day). In addition, its poor solubility in water contributes to high variability in absorption. In order to improve the solubility and bioavailability, some efforts have been made in recent years, such as the study of oridonin-solid liquid nanoparticles for injection (Zhang et al., 2005). The oral route is the most physiologically beneficial and easily accepted by patients. Therefore, it is necessary to develop alternative oral routes of administration to enhance the bioavailability of poorly water-soluble drugs, and furthermore obtain more successful therapeutic effects.

The use of self-microemulsifying drug delivery system (SMEDDS) is one of the most interesting approaches to improving the solubility, dissolution and oral absorption for poorly water-soluble drugs (Constantinides and Scalart, 1997; Hauss et al., 1998; Holm et al., 2003; Kommura et al., 2001). A commercially available SMEDDS preparation is Neoral® (cyclosporine A). Now, much more attention has been focused on SMEDDS due to its excellent efficiency in delivering poorly water-soluble drugs and achieving an increase in bioavailability. SMEDDS are isotropic mixtures of oil, surfactant, co-surfactant, and drug substance. Microemulsion can be generated rapidly upon gentle mixing with water or aqueous media. It is thought that the microemulsion is spontaneously formed by the combined action of the specific pharmaceutical excipients with low free energy. The microemulsion droplets dispersed in the gastrointestinal tract provide large surface area and promote a rapid release of dissolved form of the drug substance and/or mixed micelles

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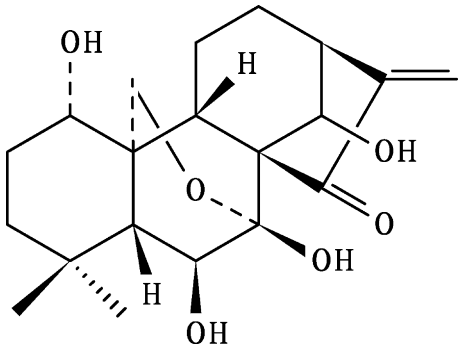

Fig. 1. Chemical structure of oridonin.

containing drug substance, and they may be also responsible for transporting the drug through the unstirred water layer to the gastrointestinal membrane for absorption. In addition to the enhanced dissolution of drugs by SMEDDS, another factor contributing to the increasing bioavailability is that lymphatic transport is responsible for a portion of the entire drug uptake as well. The lipid composition of SMEDDS may be related to facilitate the extent of lymphatic drug transport by stimulating lipoprotein formation and intestinal lymphatic liquid flux (Iwanaga et al., 2006; Porter et al., 2007). Over the past decades, SMEDDS have been extensively investigated to deliver various kinds of drugs (Cui et al., 2005; Kang et al., 2004; Kim et al., 2000; Khoo et al., 1998; Pouton, 2000; Wei et al., 2005). Only a few studies have been reported on the effective composition of traditional Chinese medicines (Cui et al., 2005; Wu et al., 2006).

The aim of our present study was to develop a SMEDDS formulation of oridonin to improve its oral bioavailability.

2. Materials and methods

2.1. Chemicals and reagents

Oridonin was purchased from Nanjing Qingze Medical Technology Development. Co., Ltd. (Nanjing, China) with a purity of 98.2%. Polyoxyethyleneglycerol triricinoleate 35 caster oil (Cremopher EL®) and Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40®) were donated by BASF, Germany. Glyceryl monolinoleate (Maisine 35-1®), Caprylic/Capric triglyceride (Labrafac CC), PEG-8 glycol caprylate (Labrasol®), diethylene glycol monoethyl ether (Transcutol P®) were provided by Gattefosse, France; isopropyl myristate (IPM), oleic acid, 1,2-propanediol, PEG-400 were from Sinopharm Group Chemical Reagent Co., Ltd. (Shanghai, China). All other chemicals used were of analytical grade.

2.2. Solubility studies

The solubility of oridonin in various oils, surfactants, and co-surfactants was measured, respectively. An excess amount of oridonin was added into each selected vehicle, and the mixture was continuously stirred for 72 h at 30 °C. After equilibrium was achieved, the mixture was centrifuged at 2500 × *g* for 20 min, and the supernatant was filtered through a membrane filter. The concentration of oridonin was determined by high-performance liquid chromatography (HPLC).

2.3. Pseudo-ternary phase diagram construction

A pseudo-ternary phase diagram was constructed by titration of four component mixtures of oil, surfactant and co-surfactant with water at room temperature. After equilibrium, the mixture was visually observed. The generated sample which was clear or slightly bluish in appearance was determined as microemulsion. A series of pseudo-ternary phase diagrams was constructed to identify microemulsion regions and the size of microemulsion region among the diagrams was compared by direct observation. The effect of various oils on the microemulsion formation was studied by constructing ternary phase diagram with individual Maisine 35-1, individual Labrafac CC, and their mixture at the ratio of 1:2, 1:1, and 2:1 as oil phase, respectively, Cremopher EL as surfactant, Transcutol P as co-surfactant. Then, the mixture of Maisine 35-1: Labrafac CC (1:1, w/w) were fixed to be as oil phase, the following studies were carried out by constructing a ternary phase diagram: (1) the influence of various surfactants on the microemulsion formation with Transcutol P as co-surfactant; (2) the influence of various co-surfactants on the microemulsion formation with Cremopher EL as surfactant; and (3) the influence of the ratio of surfactant to co-surfactant on the formation of microemulsion.

2.4. Preparation of SMEDDS

The formulation consisted of Oridonin: (Maisine 35-1: Labrafac CC, 1:1): Cremopher EL: Transcutol P (1.5:29.5: 46:23) (%, w/w). The formulations were prepared by dissolving the formulation amount of oridonin in the mixture of Transcutol P and Maisine 35-1 at 50 °C in an isothermal water bath. Cremopher EL and Labrafac CC were then added. This mixture was mixed by vortexing until a transparent preparation was obtained.

2.5. SMEDDS characterization

2.5.1. Morphological characterization

The morphology of SMEDDS was observed by transmission electron microscope (TEM) (PHILIPS TECNAI 12, Netherlands). SMEDDS was diluted with distilled water 1:25 and mixed by slightly shaking. Then, a drop of sample obtained after dilution was placed on copper grids. The excess was drawn off with filter paper. Subsequently, it was stained in 1% phosphotungstic acid solution for 30 s.

2.5.2. Determination of droplet size and ζ-potential

The droplet size/distribution and ζ-potential were determined with Nicomp™ 380 ZLS Zeta Potential/Particle sizer (PSS Nicop, Santa Barbara, CA, USA). The detection range was from 2 to 5000 nm. Each sample was analyzed in triplicate.

2.5.3. In vitro release

In vitro release of oridonin SMEDDS was tested by the method of Wu et al. (2006) with some modifications. A dialysis method was used based on Chinese Pharmacopoeia (2005 version) release test method. After Oridonin SMEDDS was instilled into the dialysis bag (MWCO 10000, Spectrum Medical Industries Inc., USA), the dialysis bag was firmly sealed with dialysis clamp and was placed in 250 ml, 0.1N HCl (containing 0.5% of Tween 80) as the dissolution medium at 37 °C. The revolution speed of the paddle was maintained at a rate of 100 rpm. One microliter samples were drawn out at the predetermined intervals, and the same volume of fresh dissolution medium was replenished. The release of oridonin from SMEDDS formulation was compared with the suspension of oridonin containing the same quantity of drug. A sample (20 μl) was injected into HPLC.

2.6. HPLC analysis

The HPLC analysis was carried out on an Agilent high-performance liquid chromatography system (HP1100, Agilent, USA). Chromatographic condition was ODS column (Kromasil C18, 250 mm × 4.6 mm, 5 μm, Dikma Technology, Shanghai, China). The mobile phase of methanol/water (45:55) was pumped at a flow rate of 1.0 ml/min. The column temperature was kept at 25 °C. The detector was set at 241 nm.

2.7. Bioavailability studies

The bioavailability experiment was designed to compare oridonin SMEDDS and oridonin suspension. The oridonin suspension was prepared according to the following methods: PEG-400 was mixed with the same volume of purified water by stirring for 30 min. The desired amount of oridonin was then added to the mixture obtained above and mixed. Subsequently, purified water was added and blended thoroughly until uniformly distributed. Male SD rats (180–250 g) were supplied by the Laboratory Animal Center of Shanghai University of Traditional Chinese Medicine. They were allocated to two groups at random. The animals were fasted for 12 h prior to the oral administration of oridonin SMEDDS and oridonin suspension with a dose of 20 mg/kg. After dosing for 0, 5, 15, 30, 45, 60, 90, 120, 240, 360, 480, and 720 min, 0.5 ml blood was collected from the retroorbital plexus with a heparinized tube. The blood samples were then centrifuged at 3000 × *g* for 10 min. The serum samples were separated and stored at −20 °C for later analysis.

The experimental procedures were approved by the institutional animal ethical committee and were in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

A 20 μl aliquot of pH 5.0 phosphate buffer was added to an aliquot of plasma. After vortex-mixing for 10 s, a 3 ml aliquot of ethyl acetate was added and vortexed for 5 min, and then sonicated for 1 min. After centrifugation at 3000 × *g* for 10 min, the organic layer was collected and 2.5 ml was transferred to a clean tube and dried under nitrogen gas at 40 °C. The residue was reconstituted with a 100 μl aliquot of methanol, and 20 μl was injected directly onto the HPLC column. The mean recovery was 93.8% with a coefficient of variation below 5%. The linear regression equation of the calibration graph of oridonin was $C = 70.03A - 58.60$ (correlation coefficient $r = 0.999\,0$). The linear range for the determination of oridonin was 25–2500 ng/ml, limit of detection (S/N > 3) was 4 ng/ml. At concentrations of 10, 25, 500 ng/ml, spiked recoveries of oridonin from rat plasma were 100.8%, 118.8%, and 93.8%, intro-day precision was 4.28%, 9.00% and 3.91%; inter-day precision was 4.24%, 9.00%, 4.80%.

Plasma concentration versus time data of oridonin for rats was analyzed using standard non-compartment analysis. The area under the plasma concentration-time curve ($AUC_{0\to t}$) from zero to the last time point was estimated by the linear trapezoidal method. The relative bioavailability (F) of SMEDDS to the suspensions was calculated using the following equation:

$$F = \frac{AUC_{test}}{AUC_{reference}} \times 100\%$$

2.8. Statistical analysis

Results are reported as means ± S.D. Kraskal–Wallis test or one-way analysis of variance followed by a post hoc (Tukey's test) was applied for statistical analysis of the effects of oil concentration, drug loading, formulation composition, dilution and mixing on droplet size and zeta potential. The pharmacokinetic parameters were statistically examined using the Mann–Whitney U-test. A value of $P < 0.05$ was considered statistically significant.

3. Results and discussion

3.1. Screening of oils and surfactants

The consideration for screening formulation of SMEDDS usually involves: the formulation composition should be simple, safe, and compatible; it should possess good solubility; a large efficient self-microemulsification region which should be found in the pseudo-ternary phase diagram, and have efficient droplet size after forming microemulsion (Constantinides, 1995; Klous et al., 2004; Kommura et al., 2001; Subramanian et al., 2004).

Appropriate vehicles should have good solubilizing capacity of the drug substance, which is essential for composing a SMEDDS. The results of solubility of oridonin in some vehicles were shown in Table 1. The components and their concentration ranges can be obtained by construction of a pseudo-ternary phase diagram with constant drug level fixed at 1.5% (w/w).

The drug loading capability is the main factor when screening the oil phase. Oridonin has the highest solubility in Maisine 35-1, followed by Labrafac CC as shown in Table 1. Their phase behavior was compared by constructing pseudo-ternary phase diagram. The maximum fields of self-microemulsion were obtained when the mixture of Maisine 35-1 and Labrafac CC in the ratio of 1:1 was used as oil phase. Hence, the mixture of Maisine 35-1 and Labrafac CC in the ratio of 1:1 was selected as oil phase.

Table 1
Solubility of oridonin in various vehicles at 25 °C ($n = 3$)

Vehicle	Solubility (mg/ml)
Maisine 35-1	7.00 ± 0.93
Labrafac CC	0.41 ± 0.08
IPM	0.16 ± 0.03
Oleic acid	0.39 ± 0.15
Ethyl oleate	0.30 ± 0.05
Cremopher EL	9.46 ± 0.17
Labrasol	23.81 ± 1.83
Cremopher RH40	5.90 ± 0.60
Transcutol P	54.10 ± 1.32
1,2-Propanediol	31.92 ± 2.01
PEG-400	37.35 ± 1.26

Non-ionic surfactants were used in most of the investigation about SMEDDS because they are less toxic and less affected by pH and ionic strength. The self-microemulsion region of both Cremopher RH40 and Cremopher EL was larger than that of Labrasol. Cremopher RH40 formed a larger gel-like structure region than Cremopher EL, and required a longer time to disperse. This was of concern in terms of affording efficient and rapid drug release. Therefore, the desirable surfactant should be Cremopher EL.

As to the selection of co-surfactant, 1, 2-propanediol and PEG-400 have relatively higher hydrophilic ability, increasing the risk of destroying the microemulsion compared with Transcutol P. In addition, Transcutol P provided the highest drug solubility among all vehicles tested in our studies. Therefore, it is reasonable to select Transcutol P as the co-surfactant.

The phase diagrams of the systems containing Maisine 35-1: Labrafac CC (1:1, w/w), Cremopher EL, and Transcutol P were shown in Fig. 2. Although it is considered that the large content of oil in the formulation will be beneficial to the SMEDDS, a proper droplet size distribution is also an important factor for selecting a suitable self-microemulsifying vehicle. The effect of the oil concentration on the droplet size was investigated as well. The droplet size increased from 24 to 110 nm when the oil concentration increased from 20 to 50%. According to Fig. 3, 30% oil should be expected in the formulation.

The ratio of surfactant to co-surfactant was very effective to a stable and efficient SMEDDS formation. The phase diagrams were constructed at the ratio of surfactant/co-surfactant 4:1, 2:1, 1:1, 1:2, 1:4 (w/w). The gel-like region was found to become large with the increasing concentration of Cremopher EL, while the self-microemulsifying region expanded with the ratio of Transcutol P increasing. The maximum self-microemulsifying region was to be at the ratio of 1:4. However, the drug pre-

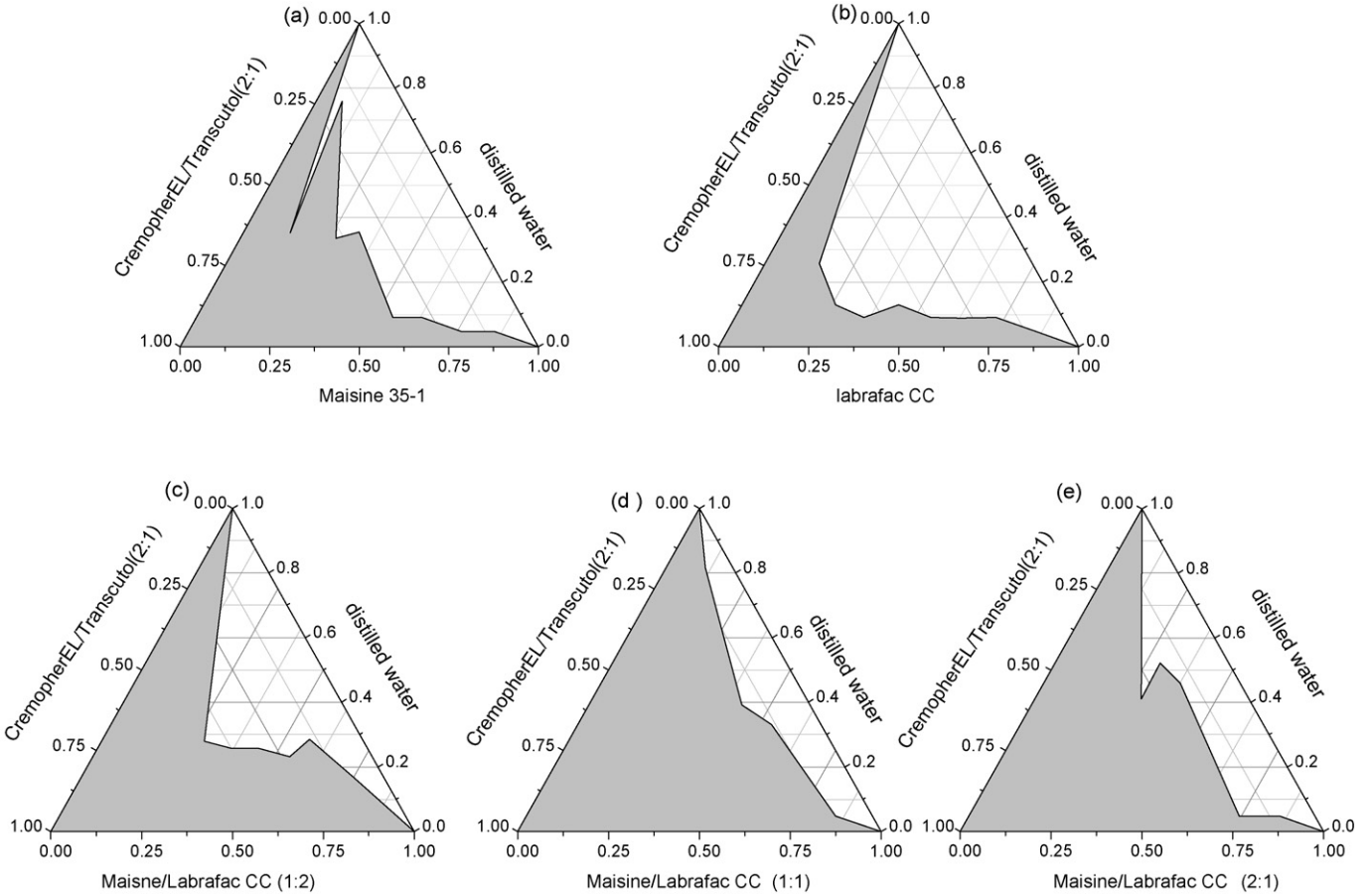

Fig. 2. Pseudo-ternary phase diagrams of the formulations composed of various oil, Cremopher EL and Transcutol P dispersed with distilled water at 37 °C. The oil phases were as follows: Maisine 35-1 (a), Labrafac CC (b), Maisine 35-1:Labrafac CC (1:2) (c), Maisine 35-1:Labrafac CC(1:1) (d), and Maisine 35-1:Labrafac CC (2:1) (e). The shadow area represents microemulsion region.

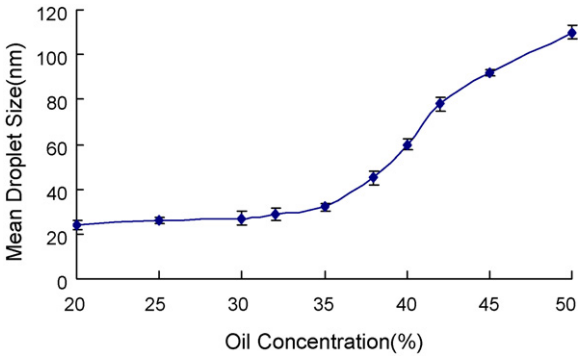

Fig. 3. Effect of oil concentration on the droplet size ($n = 6$). (The ratio of surfactant to co-surfactant was 1:1.)

cipitation was observed after several hours at the ratio of 1:2 and 1:4. The influence of the different ratios of surfactant (Cremopher EL) to co-surfactant (Transcutol P) on the droplet size was also investigated. There were minor differences in mean droplet size when the ratio of co-surfactant increased from 10 to 45%. Co-surfactant will be beneficial to form microemulsion at a proper concentration range. However, excessive amount of co-surfactant will cause the system to become less stability for its intrinsic high aqueous solubility and lead to the droplet size increasing as a result of the expanding interfacial film. (Lawrence and Rees, 2000; Zhang et al., 2004). Hence, the optimal ratio of surfactant to co-surfactant was selected to be 2:1.

Based on our results, a three-component SMEDDS formulation was established: 30% mixture of Maisine 35-1 and Labrafac CC (1:1) as oil, 46.7% Cremopher EL as surfactant and 23.3% Transcutol P as co-surfactant. The pseudo-ternary phase diagram was shown in Fig. 4.

3.2. SMEDDS characterization

3.2.1. Morphological characterization

The oridonin SMEDDS turned into microemulsion when diluted with distilled water. The TEM picture was shown in

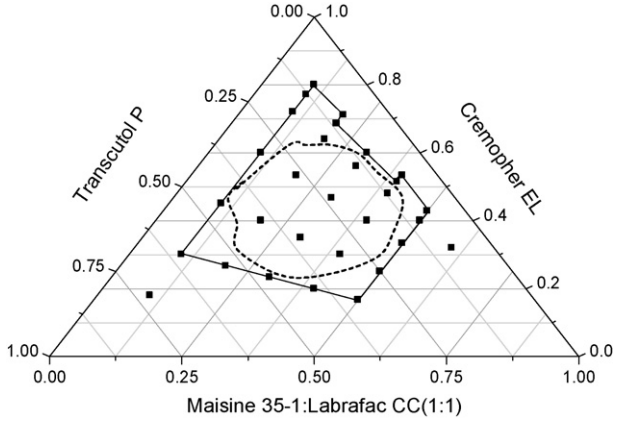

Fig. 4. Pseudo-ternary phase diagram of SMEDDS formulation composed of Maisine 35-1/Labrafac CC (1:1) as oil, Cremopher EL as surfactant and Transcutol P as co-surfactant. The solid line area represents the area where a microemulsion is formed and the dotted line area represents the efficient self-microemulsification.

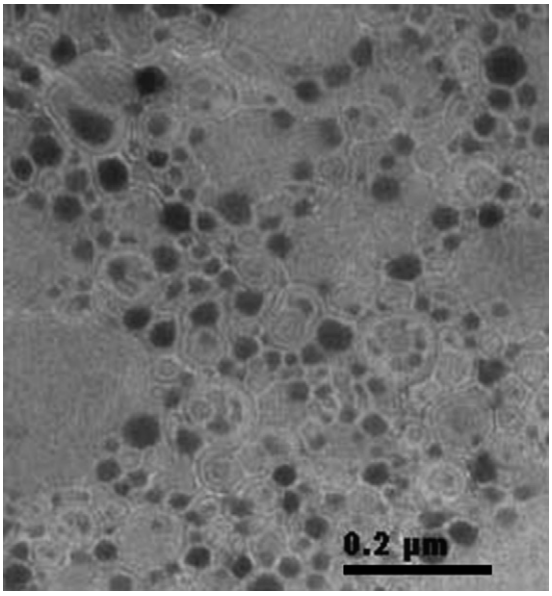

Fig. 5. TEM photo of oridonin microemulsion (×43,000).

Fig. 5. The microemulsion droplets were observed to be spherical.

3.2.2. Droplet size analysis

Droplet size distribution following self-microemulsification is a critical factor to evaluate a self-microemulsion system. Droplet size is thought to have an effect on drug absorption as has been illustrated in several papers. The smaller the droplet size, the larger the interfacial surface area will be provided for drug absorption (Gershanik and Benita, 2000; Kang et al., 2004; Pouton, 2000). In our study, we investigated several variables on droplet size including dilution volume, different media, drug concentration (drug loading), and dispersing method. The average droplet size of microemulsion dispersed from the oridonin SMEDDS was within 100 nm and showed Gaussian distribution.

The effect of dilution on droplet size in distilled water was measured. When the dilution time was 1000-fold, the droplet size seemed to be unchanged, which revealed that the microemulsion formed upon dilution was as large as 1000 times capable of keeping oridonin solubilized.

As the drug loading increased from 0.2 to 2.5%, the droplet size remained almost unchanged, which indicated that the drug loading had no obvious effect on droplet size in water.

The effect of medium on droplet size was also investigated in our study. When the SMEDDS dispersed in distilled water, 0.9% NaCl, 0.1N HCl and pH 6.8 phosphate buffer, the resulted droplet size was 24.1 ± 3.6 nm, 25.6 ± 1.7 nm, 25.9 ± 1.8 nm and 25.7 ± 3.3 nm, respectively. There is no significant difference among the four different media, which demonstrated that the formulation was not affected by pH and the ionic strength.

The effect of the various mixturing ways on the droplet size was measured. Different mixturing ways including oscillate, whisk (25 rpm, 50 rpm, 100 rpm) and swirl seem to have no obvious effect on droplet size since the resulted droplet size varied from 23.9 ± 2.9 nm to 24.4 ± 2.3 nm. This result predicts stable SMEDDS can be formed under gastrointestinal peristalsis.

3.2.3. ζ-Potential analysis

Generally, an increase of electrostatic repulsive forces between microemulsion droplets prevents the coalescence of microemulsion droplets. On the contrary, a decrease of electrostatic repulsive forces will cause phase separation. Oridonin SMEDDS was diluted with distilled water, 0.9% NaCl, 0.1N HCl and pH 6.8 phosphate buffer, and the resulted zeta potential was -4.16 ± 0.33 mV, -3.54 ± 0.41 mV, 4.88 ± 0.29 mV, and -5.97 ± 0.47 mV, respectively. There is no marked difference in the absolute ζ-potential value among the four media. It's interesting that the surface charge was positive for the droplets in 0.1N HCl. This result indicated this formulation would reach a positive zeta potential at physiological pH. Several studies have reported that the zeta potential played an important role in the interactions with mucus of the gastrointestinal tract (Gershanik et al., 2000; Wei et al., 2005). According to the reports, the positive charged droplets could have better interaction with the mucus of the gastrointestinal tract, since the intestinal cell interior carry negative charges with the presence of mucosal fluid. Because the droplets in 0.1N HCl have a positive potential, they are likely to facilitate the intestinal absorption of oridonin. The reason why the droplets in 0.1N HCl carry the positive charge is still unclear. It needs further investigation.

3.2.4. Cloud point measurement

The cloud point is an essential factor in the SMEDDS consisting of non-ionic surfactants, and it is responsible for the successful formation of a stable microemulsion (Itoh et al., 2002). When the temperature is higher than the cloud point, an irreversible phase separation will occur and the cloudiness of the preparation would have a bad effect on drug absorption, because of the dehydration of the polyethylene oxide moiety. Hence, the cloud point for SMEDDS should be above 37 °C, which will avoid phase separation occurring in the gastrointestinal tract. Oridonin SMEDDS was diluted with water in the ratio of 1:250, and the sample was placed in a water bath with the temperature increasing gradually, at 5 °C intervals (or at 2 °C intervals when approaching the cloud point), spectrophotometric analysis was carried out to measure the sample transmittance using an empty glass test tube as a blank. The cloud point was found to be 72 °C. Therefore, it would suggest a stable microemulsion of oridonin can be formed at physiological temperature *in vivo*.

3.2.5. In vitro release

To understand the characteristics of drug release from SMEDDS, an *in vitro* release study was carried out. When SMEDDS encountered aqueous media, the drug existed in the system in different forms including a free molecular form, or mixed in the micelles or in the microemulsion droplets. Under this circumstance, it is necessary to separate the isolated drug molecules from those trapped by micelles or microemulsions for a real *in vitro* release test. Therefore, it is not rational to use the routine release approach in this case. Recently, dialysis method was applied for SMEDDS *in vitro* release study (Wu et al., 2006; Sheikh et al., 2007). The profile of drug release was illustrated in Fig. 6. In spite of a slightly higher release of drug from the suspension than that from SMEDDS in the first 2 h, the release of drug from SMEDDS was markedly boosted compared with that of drug suspension in the following 10 h. In the case of SMEDDS, more than 85% of oridonin was released during the first 6 h and the accumulated amount of drug release in 12 h was 100.2%, indicating a complete release.

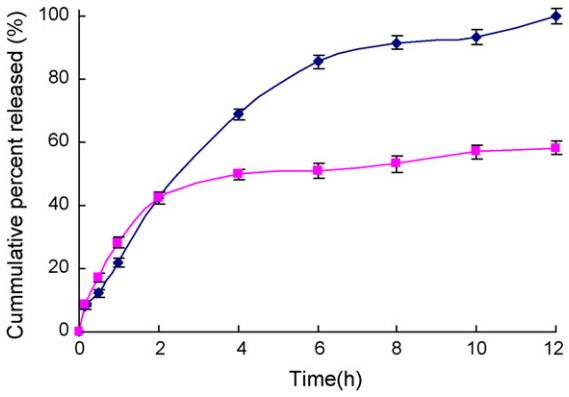

Fig. 6. *In vitro* release profile of oridonin from SMEDDS and suspension in 0.1 N HCl (♦, SMEDDS; ■, suspension).

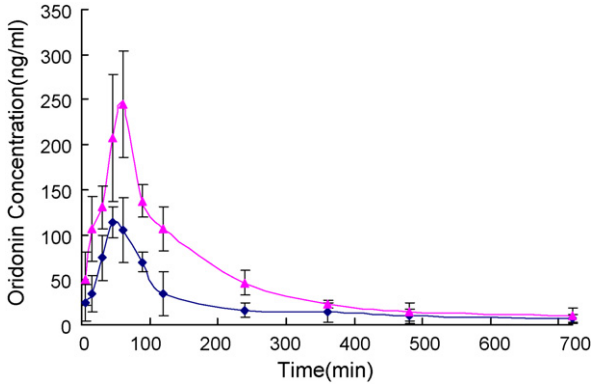

Fig. 7. Plasma concentration profile of oridonin after oral administration of SMEDDS (triangles) and the suspension (diamonds) in rats ($n = 3$ and 20 mg/kg).

3.3. Bioavailability study

The *in vivo* pharmacokinetic behavior of oridonin with SMEDDS and suspension were investigated. Their pharmacokinetic parameters were compared in rats. Fig. 7 shows the plasma profiles of oridonin after gavage administration of the two preparations. The pharmacokinetic parameters are given in Table 2. The C_{max} and $AUC_{0\rightarrow t}$ of the SMEDDS were significantly higher than those of the suspension. The relative bioavailability

Table 2
Relative bioavailability and pharmacokinetic parameters of oridonin after oral administration oridonin SMEDDS and suspension to the rats ($n = 3$)

	SMEDDS	Suspension
$AUC_{0\rightarrow 12h}$ (ng/ml min)	611.71 ± 35.47	277.79 ± 104.78
$AUC_{0\rightarrow\infty}$ (ng/ml min)	639.21 ± 53.62	297.94 ± 121.94
C_{max} (ng/ml)	244.89 ± 59.57	123.49 ± 25.25
T_{max} (min)	60.0 ± 0.31	50.0 ± 8.66
Relative bioavailability (%)	220.21	–

of SMEDDS was approximately 2.2-fold compared with the suspension. Therefore, SMEDDS might be a promising approach to the oral delivery of Oridonin. When evaluating the *in vivo* behavior of drug substance, it is necessary to consider the following two aspects: one concerns the factors influencing the drug absorption *in vivo*, the other concerns the formulation factors influencing its *in vitro* release. As for SMEDDS, it is rational to deduce that the factors influencing the drug *in vivo* absorption rather than the improved *in vitro* release may contribute to the enhanced absorption. For a poorly water-soluble drug, the absorption is often inadequate due to an insufficient dissolution in the gastrointestinal tract. Therefore, the dissolution process might be a critical factor influencing the adsorption. Once the SMEDDS encounters the gastrointestinal tract, the spontaneous formation of a microemulsion presents the drug in a dissolved form and the dose from the drug in the soluble form will be beneficial to enhance absorption. The drug absorption mechanisms include transcellular routes and paracellular routes, which are determined by the properties of the drug itself and its molecular weight. In most cases, the hydrophobic drugs with low molecular weight are absorbed by the transcellular route. They are not easily absorbed by the paracellular route since the tight junction is the absorption barrier. However the drug absorption behavior can be facilitated by the formation composition in SMEDDS, especially by the surfactant, which can reduce the interfacial surface tension and enhance penetration of the drug to the epithelial cells. The surfactant also acts by dispersing the lipid formulation in the gastrointestinal tract into small droplets with a large interfacial surface area, which may also be responsible for absorption. Furthermore, SMEDDS, a lipid-based formulation, is considered to be partially absorbed via the lymphatic route as well. That may reduce the opportunity for hepatic first pass metabolism and therefore enhance the bioavailability of drugs.

The animal model may be of concern when studying SMEDDS. Since the dynamic process *in vivo* would be responsible for the emulsification progress. In this study, rats were used due to their low cost and relatively facile accessibility. However, it is not clear whether the amount of fluid present in the rat stomach might be insufficient to emulsify the administered dose of SMEDDS. The influence of the animal model on the bioavailability still needs to be investigated, and it would be interesting to study the bioavailability of oridonin from SMEDDS in a larger animal, such as rabbit or dog.

4. Conclusion

A SMEDDS containing poorly water-soluble drug, oridonin, was formulated for oral application. The components and their ratio ranges for the formulation of SMEDDS were obtained by solubility study, pseudo-ternary phase diagram construction, and droplet size analysis. The optimum formulation of the SMEDDS consisted of 30% mixture of Maisine 35-1 and Labrafac CC (1:1), 35% Cremopher EL, and 35% Transcutol P, which had sufficient drug loading, rapid self-microemulsification in aqueous media, and forming droplet size in the range of microemulsion. The formulation showed greater extent of absorption than the suspension. The relative bioavailability of the SMEDDS to suspension was 220.21%. These results suggested the potential use of SMEDDS for oral administration of oridonin.

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