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Preparation and characterization of nanostructured lipid carriers loaded traditional Chinese medicine, zedoary turmeric oil

Xiu-Li Zhao, Chun-Rong Yang, Kai-Liang Yang, Ke-Xin Li, Hai-Yang Hu and Da-Wei Chen

School of Pharmacy, Department of Pharmaceutics, Shenyang Pharmaceutical University, Shenyang, Liaoning, PR China

Abstract

Background: The objective of this work was to study the preparation and characteristics of zedoary turmeric oil (ZTO), a traditional Chinese oily medicine, loaded with nanostructured lipid carriers (NLCs). *Method*: Aqueous dispersions of NLC were successfully prepared by melt-emulsification technique using Crodamol SS as the solid lipid, Miglyol 812N as the liquid oil, and soybean phosphatidylcholine (SbPC) as the emulsifier. Properties of NLC such as the particle size and its distribution, the transmission electron microscope (TEM), drug entrapment efficiency (EE), and drug release behavior were investigated, respectively. The Germacrone blood concentration after intravenous administration of ZTO–NLC was determined and compared with that of ZTO-injection. *Result*: As a result, the drug EEs were improved by adding the liquid lipid into the solid lipid of nanoparticles (SLNs). In vitro drug release experiments indicated that the prepared NLC could enhance the drug release rate over the SLN, and the drug release rate could be adjusted by the liquid lipid content in lipid nanospheres. X-ray and differential scanning calorimetry (DSC) measurements revealed that imperfect crystallization occurred in the inner core of the NLC particles. *Conclusion*: The results suggest that the presented NLC system might be a promising intravenous dosage form of water-insoluble oily drugs.

Key words: *In vitro drug release; inner structure; melt-emulsification technique; nanostructured lipid carrier; pharmacokinetics; zedoary turmeric oil*

Introduction

The use of nanospheres as drug-carrier system has received great attention in recent years. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are two main types of lipid nanospheres[1]. Both carrier types are based on solid lipid; however, they can be distinguished by their inner structure. The advantages of SLN are reported to be produced on a large industrial scale, obtain sustained release, with low toxicity and good biodegradation, and can effectively target specific tissues[2–4]. However, there are also some potential limitations associated with SLN, that is, limited drug loading capacity, low drug entrapment efficiency (EE), drug expulsion during storage because of the crystallization of lipid matrix, and so on[5]. To overcome the limitations of SLN, NLCs are developed in recent years. Compared with consisting of pure solid lipids in SLN, NLC composed of a certain percentage of additional liquid lipid leading to imperfections in the crystal lattice of nanoparticles, thus leading to improved drug loading capacity and reduced drug expulsion during storage[6–8].

Zedoary turmeric oil (ZTO), a volatile composition extracted from the dry rhizome of the traditional Chinese medicinal herb Curcuma zedoaria, which is good in protecting against liver injury, tumor suppressing, antibacterial, increases white blood cells, and has antithrombotic activity[9–11], has long been used as a folk medicine in China. From ZTO, including furanodiene, germacrone, curdione, neocurdione, curcumenol, isocurcumenol, aerugidiol, and zedoarondiol, some hepatoprotective sesquiterpene compounds were found to present potent protective effect on D-galactosamine/lipopolysaccharide-induced liver injury in mice[12,13].

Address for correspondence: Prof. Da-Wei Chen, School of Pharmacy, Department of Pharmaceutics, Shenyang Pharmaceutical University, PO Box 42, 103 Wenhua Road, Shenyang, Liaoning 110016, PR China. Tel: +86 024 23986308. E-mail: raura3687yd@163.com

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However, the common side effects of ZTO were upper gastrointestinal (GI) irritation and poor water solubility resulting in low oral bioavailability, which might be avoided by making into intravenous formulations. On the contrary, in clinic, the injection of ZTO is formulated in a vehicle composed of a mixture of Tween 80 and dehydrated alcohol. Tween 80 has been reported to exist and is safe for injection. An intravenous formulation with a high degree of safety and targeting would, therefore, be highly desirable.

The ultrasonic-solvent emulsification technique is a common method for the preparation of lipid nanospheres[14,15]. However, the organic solvent used in the process could affect the safety of the intravenous formulation. In this article, the melt-emulsification technique was employed to prepare NLC. This method had two advantages: the one is no need for organic solvent and the other is simple preparation procedure.

In this study, ZTO-loaded NLCs were successfully prepared for parenteral application by the melt-emulsification technique. The feasibility of using ZTO-loaded NLCs as an alternative parenteral formulation for ZTO was demonstrated through characterization of particle size, drug EE, and in vitro drug release behavior. The differential scanning calorimetry (DSC) and X-ray experimental results revealed that NLC particles were quite different to the SLN particles in their inner microstructures. This difference between NLC and SLN particles shows that the NLC may have a good drug loading capacity for parenteral application of ZTO. Pharmacokinetics in vivo between drug-loaded NLC and ZTO injection were further evaluated.

Experimental

Materials

ZTO and ZTO injection were provided by Zhejiang Ruian Pharmaceutical Co. (Zhejiang, China). The germacrone standards were purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Soybean phosphatidylcholine (SbPC) was obtained from Shanghai Taiwei Pharmaceutical Co. (Shanghai, China). Crodamol SS (Cetyl Esters Wax NF) and Miglyol 812N (caprylic/capric triglycerides) were kindly donated by CRODA (Croda chemicals Ltd., Goole, East Yorkshire, UK) and SASOL Chemie GmbH (Sasol Ltd., Hamburg, Germany), respectively. The water used for all experiments was distilled water.

Preparation of NLC

For the preparation of NLC with different Miglyol 812N content by melt-emulsification method, 200 mg mixture of lipid and liquid lipid were mixed and melted at 55°C. In the experiments, the total amount of lipid was kept constant and only the proportion of the liquid oil in the total lipid was changed from 0 to 30 wt.%. One hundred milligrams of drug was then dispersed in the mixture of melt lipid. The melted mixture of lipid and drug was then dispersed in 10 mL 3 wt.% surfactant solution (heated up to 55°C), using a mechanical stirrer to form a primary emulsion. The warm primary emulsion was further treated for 4 minutes (work 5 seconds and stand 5 seconds) by a Lab ultrasonic cell pulverizer (JY92-H; Ningbo Scientz Biotechnology Co., Ltd., Ningbo, China) at 600 W to form miniemulsion. The miniemulsion was rapidly cooled by immersing beaker into icy water (0°C). The dispersion was agitated continuously for 2 hours and then filtrated through 0.22 μm membrane to yield a uniform dispersion of NLC. The formulations used were shown in Table 1.

Freeze-drying and redispersion

The SLN and NLC in suspension were frozen at −20°C with the presence of 10% trehalose in a deep-freezer (Sanyo Ultra Low Temperature Freezer MDF-192, Sanyo Ltd., Tokyo, Japan) overnight in glass vials. The freeze-drying process was carried out at −55°C at a pressure of 10^{-4} Torr during 36 hours. Then, the powders were collected and stored at 4°C. The dry powder was used to determine the thermal analysis. Suspensions were reconstituted in 2 mL of pure water under vortex agitation.

Measurement of particle size and zeta potential

The mean diameter of SLN and NLCs in the dispersion was determined by a Nicomp 380-Submicron Particle Sizer (Particle Sizing Systems, Santa Barbara, CA, USA) at a fixed angle of 90° at 25°C. The particle size analysis data were evaluated using the volume distribution. Zeta potential measurement was carried out using zeta potential analyzer (Delsa 440SX; Beckman Coulter Co. Ltd., South Kraemer Boulevard, Brea, CA, USA) at the same temperature. Before measurement, NLC dispersions were diluted 20-fold with the distilled water for size determination and zeta potential measurement. All the measurements were performed in triplicate.

Table 1. Recipes for the preparation of ZTO–NLC (wt.%).

Ingredient	A	B	C	D	E
ZTO	1	1	1	1	1
Crodamol SS	2	1.8	1.6	1.4	2.1
Miglyol 812N	–	0.2	0.4	0.6	0.9
Soybean lecithin	2	2	2	2	2
Water	95	95	95	95	94

Transmission electron microscopy

Transmission electron microscope (TEM) of NLCs was examined using an electronic transmission microscope (CM10, Philips Co. Ltd., Tokyo, Japan). After diluting 20-fold with the distilled water, the samples were negatively stained with 1.5% (w/v) phosphotungstic acid for observation.

Stability studies

The lyophilized ZTO–NLC powder was stored in bottles at 4°C for 12 months. By redispersion, the content of ZTO, the average size, zeta potential, and EE were studied.

Drug entrapment efficiency and drug loading

The concentration of germacrone (an indexical component found in ZTO, 10.75%, w/w) was measured using a high-performance liquid chromatography (HPLC) method at 245 nm recorded in Ch. P. (2005 ed.). As for the determination of drug EE and load content of NLC, 1 mL NLC dispersion was separated by Sephadex G-50 column (SinoAmerican Biotechnology Co., San Francisco, CA, USA). The parts of the outflow with opalescence and metered volume to 25 mL were collected, 2 mL of which was dissolved in 3 mL tetrahydrofuran and the eluant added to 10 mL, and the lipid was preferentially precipitated by vortexing. After centrifugation ($1062.5 \times g$ for 15 minutes), the drug content in the supernatant was measured by HPLC. Another 1 mL NLC dispersion was metered volume to 25 mL directly and then 2 mL of which was treated and analyzed as described above.

The drug (EE) and drug load content (LD) of NLCs were calculated by Equations (1) and (2),

$$\text{Entrapment efficiency } (\%) = \frac{W_s}{W_{total}} \times 100\% \quad (1)$$

$$\text{Load content } (\%) = \frac{W_s}{W_{lipid}} \times 100\%, \quad (2)$$

where W_s is the amount of germacrone in the NLCs, W_{total} the amount of germacrone used in formulation, and W_{lipid} the weight of the vehicle.

DSC analysis

DSC analysis was performed using a Thermal Analysis System TA-60WS (Shimidazu Co., Kyoto, Japan). A scan rate of 10°C/min was used in the temperature range 30–290°C. Analysis was performed under a nitrogen purge, standard aluminum sample pans (PerkinElmer Life and Analytical Sciences Inc., Walthana, MA, USA) were used, and an empty pan was used as reference.

X-ray analysis

Crystalline structures of the particles were investigated using an X-ray diffractometer (D8 Advance, Bruker Axs, GmbH, Karlsruhe, Germany). Diffractograms were performed from the initial angle $2\theta = 0°$ to the final angle $2\theta = 50°$. A Cu Kα radiation source was used, $\lambda =$ 1.5418 nm, and the scanning rate was 0.3 seconds/step.

In vitro release study

To ensure sink condition, the drug release from NLCs was performed in 1.2% Tween 80 phosphate buffer (pH 7.4) using the dialysis bag method. The dialysis bag retains NLCs and allows the free drug into the dissolution media with a cutoff of 8000–14,000. The bags were soaked in double-distilled water for 12 hours before use. Two milliliters of NLC dispersion (1.0 mg/mL of Germacrone) was poured into the bag with the two ends fixed by clamps. The bags were placed in a conical flask and 150 mL of receiving phase was added. The conical flasks were placed into a thermostatic shaker (HZQ-C; Haerbin Dongming Medical Instrument Factory, Haerbin, China) at 37°C at a rate of 140 times per minute. At 0.5, 1, 2, 4, 6, 8, 10, 24, 48, 72, and 96 hours after test, the medium in the conical flask was completely removed by filtration for analysis and fresh dialysis medium was then added to maintain sink conditions. The filtrate was analyzed by the HPLC method. All the operations were carried out in triplicate.

In vivo study

Wistar rats (male and female, 12 weeks old, 200 ± 30 g) were provided by the Animal Center of Shenyang Pharmaceutical University (the experimental protocol was approved by the Ethics Review Committee for Animal Experimentation of Shenyang Pharmaceutical University). Before administration, the rats were fasted overnight but were allowed free access of water ad libitum. The ZTO–NLC or ZTO injection was administrated to rats (100 mg/kg, calculated by ZTO) through the tail vein. Blood samples (~0.4 mL) were drawn by puncture of the retroorbital sinus at selected times. Blood samples were collected in heparinized tubes and stored at –20°C as soon as possible until assay. Specimens were thawed and allowed to reach room temperature before analysis.

The noncompartmental pharmacokinetic parameters such as area under the drug concentration–time curve, biological half-time ($t_{1/2}$), mean resident time, total clearance (CL), and apparent volume of distribution at steady state (V_{ss}) were calculated based on the reported

method[16]. Levels of statistical significance ($P < 0.05$) were assessed using the Student's *t*-test between the two means for unpaired data. All results were expressed as mean ± SD.

Results and discussion

Preparation of NLCs

The ZTO-loaded NLC with different Miglyol 812N content was prepared by melt-emulsification technique. The preparation recipes and the properties of resultant ZTO-loaded NLC and SLN are shown in Tables 1 and 2. As shown in Table 2, the results demonstrated that the liquid lipid (Miglyol 812N) concentration affected the NLCs characteristics. The SLN was produced in the formula A for no liquid lipid in it. In others formulations, the Miglyol 812N was added as a liquid lipid to produce NLCs. Comparing with the results of SLN (formula A), the mean particle size of resulted NLCs (formulas B, C, and D) was decreased from 305.3 to 128.2 nm by the incorporation of 10–30 wt.% Miglyol 812N in given total lipid (2%). The smaller particle size of NLC was contributed to the lower surface tension of mixed lipid matrix than solid lipid matrix, which has been reported by Hu et al.[17]. As for the zeta potential, both SLN and NLCs presented a negative surface charge that would enhance the stability of the systems. There were no significant differences in all formulas. Moreover, the EE of ZTO–NLC produced by 10–30 wt.% liquid lipid relative to the total lipid was increased from 88.2 to 94.2 wt.%. The higher the concentration of the liquid lipid, the higher the drug EE. The higher solubility of drug in liquid lipid was probably the main factor for the improvement of EE. The results consist of previous reports that the incorporation of liquid lipids to solid lipids could lead to massive crystal order disturbance, and the resulting matrix of lipid particles indicates great imperfections in the crystal lattice and leaves enough space to accommodate drug molecules, thus leading to improved EE, drug load, and reduced mean particle size[18]. To demonstrate this hypothesis, DSC and X-ray analysis were performed later. Meanwhile, as for volatility and thermoinstability of the ZTO, incorporation of liquid lipid into solid lipid matrix could decrease efficiently the melting point of the lipid (data were not shown) and subsequently decrease the temperature of the production. In formulas D and E, at the same ratio Crodamol SS and Miglyol 812N when the total amounts of the mix lipid increased from 2 to 3%, the mean particle size increased slightly, and there were no significant effects on the EE of the NLCs. The results show that ZTO has a high EE and load content in NLCs. These results may have contributed to the better compatibility between oily ZTO and mix lipid.

Table 2. Mean particle sizes, zeta potentials, and entrapment efficiency (EE) of NLCs.

Formulation	Mean diameter (nm)	Zeta potential (mV)	EE (%)
A	399.0 ± 14.6	−28.4 ± 0.9	81.1 ± 0.4
B	305.3 ± 13.8	−27.8 ± 0.8	88.2 ± 0.5
C	168.8 ± 9.8	−28.7 ± 1.1	92.7 ± 0.3
D	128.2 ± 9.4	−29.6 ± 1.3	94.2 ± 0.4
E	182.6 ± 104	−29.4 ± 0.8	92.8 ± 0.5

TEM of NLC

To provide information on the morphology and sizes of the particles, TEM were used to take photos of the blank-NLC (formula D without ZTO) and ZTO–NLC (formula D). There were no significant difference between blank-NLC and ZTO–NLC. TEM shows that the particles had spherical or ellipsoidal shapes (Figure 1). No drug oily drop was visible in TEM, and the size as determined from TEM correlated well with the results from the particle sizer.

Storage stability of ZTO–NLCs

Table 3 gives the data of content, EE, zeta potential, and particle sizes of ZTO–NLCs after 0, 6, and 12 months of storage at 4°C. The freeze-dried samples (formula D) were readily redispersed in water under mechanical stirring at the dispersion ratio also after storage of 1 year. ZTO–NLCs suspension showed sufficient long-term stability with no significant changes of mean diameter or drug leakage ($P > 0.05$). There was also no visible aggregation in system during storage. According to the in vitro release profiles of the ZTO–NLCs after 1 year storage, no significant changes have been observed (data were not shown).

DSC analysis

DSC measurements allows for the study of the melting and crystallization behavior of crystalline materials like lipid nanospheres, because different lipid modifications possess different melting points and melting enthalpies[19–22]. The main purpose of this measurement was to detect whether the crystallinity was different in the lipid matrices because of their compositions. Figure 2 presents the DSC curves. The enthalpy and crystallinity of each sample were listed in Table 4. The result showed that, compared with bulk materials (Crodamol SS), crystallinity and enthalpy of all samples in nanospheres were lower than initial lipid, and the lowest one was formula D in which the ZTO was incorporated; it indicated that the melting of the less-ordered crystals or amorphous solids requires much less energy than

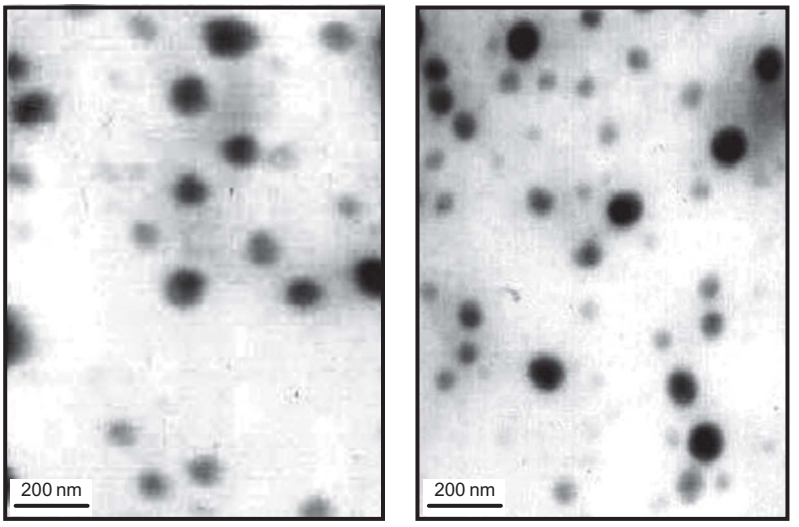

Figure 1. TEM images of blank-NLC and ZTO–NLC particles: (a) blank-NLC (formula D without ZTO); (b) ZTO–NLC (formula D, 30% Miglyol 812N).

Table 3. Effects of storage time (at 4°C) on particle size and entrapment efficiency (EE) of ZTO–NLC ($n = 5$, $x \pm s$).

Conditions	Time (months)	Content (%)	EE (%)	Zeta potential (mV)	Size (nm)
4°C	0	100	94.2 ± 0.4	−29.6 ± 1.3	128.8 ± 9.4
	6	98.7	93.7 ± 0.8	−29.1 ± 0.9	132.3 ± 31.9
	12	97.7	93.2 ± 1.2	−28.9 ± 1.1	126.7 ± 20.5

crystalline substances that need to overcome lattice forces[23]. Furthermore, with incorporation of Miglyol 812N, blank-NLC (blank-formula D) should be less ordered compared to blank-SLN (blank-formula A). In other words, adding Miglyol 812N to the SLN particles decreases the crystallinity and enthalpy in the lipid matrix. NLCs were used to change the perfect crystal structure of solid lipid. A highly disordered configuration of lipids would improve the drug loading and EE.

To compare the crystallinity between the developed formulations, a useful parameter is the crystallinity (C%), which is defined as the percentage of the lipid matrix that has recrystallized during storage time. The C% can be calculated according to the following equation[24,25]:

$$C\% = \frac{\text{Enthalpy}_{\text{Freeze-dried NLC}}}{\text{Enthalpy}_{\text{Bulk}}} \times 100\%$$

X-ray analysis

To confirm hypothesis of DSC, the inner structures of the lipid nanoparticles were studied by X-ray diffraction[26,27]. The X-ray diffraction patterns of the lyophilized blank-SLN powders, blank-NLC powders, ZTO–NLC powders, and physical blend of ZTO–NLC formulation are displayed in Figure 3. The diffraction curve of physical blend of ZTO–NLC formulation is different from that of the SLN and NLC. From Figure 3, both solid lipid Crodamol SS and trehalose have sharp peaks at 2θ=21.5° and 23.6°, respectively, indicating the crystalline nature of Crodamol SS and trehalose. Compared to the blank-SLN (blank-formula A), the peak intensities of both the blank-NLC (blank formula D) particles and ZTO–NLC (formula D) were weaker at 2θ=21.5°, indicating that the degree of the crystallinity is lower in the NLCs than in the SLN. Furthermore, there is a significant difference between the diffraction patterns of SLN and NLC particles. When 2θ equals 21.5°, SLN shows a sharp peak whereas the NLC displays a weak one, and in the same position ZTO–NLC has the weakest one. For the weakened peaks at 21.5° in both ZTO–NLC and blank-NLC, the peak at 21.5° has been owned to Crodamol SS. However, there was no obvious difference of the peak intensities at 2θ=23.6°. It was because the trehalose concentration consistent in the different formulations. Incorporation of the liquid oil does not change the position of the signals but weakens their intensity. These differences may be due to the more ordered structure of SLN in comparison to that of NLC particles. The lipid exists in a lower degree of

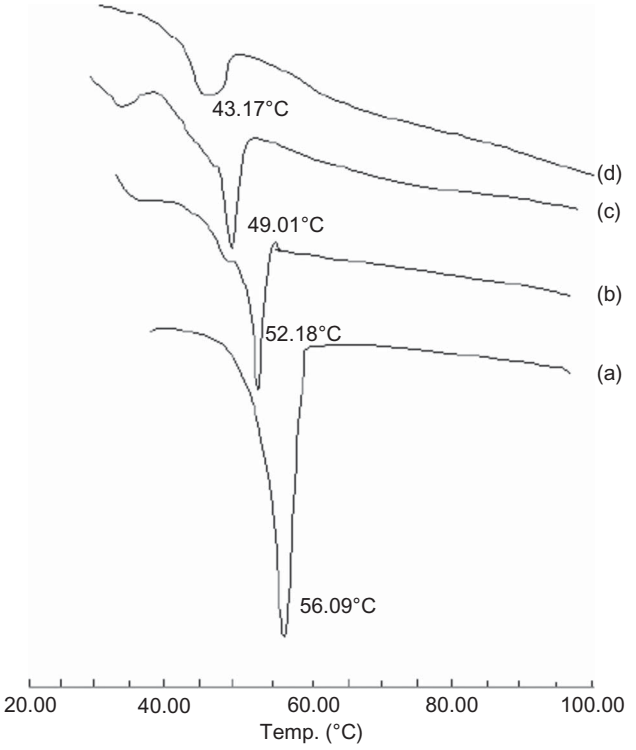

Figure 2. Differential scanning calorimetry curves (a) bulk (Crodamol SS); (b) blank-formula A (0 wt.% Miglyol 812N); (c) blank-formula D (30 wt.% Miglyol 812N); and (d) formula D (30 wt.% Miglyol 812N).

crystallinity state in the NLC whereas the Crodamol SS in SLN is higher crystallized. These results indicate that the NLC particles produced by the incorporation of Crodamol SS into SLN own a less-ordered structure. In comparison to SLN with the same lipid content, NLC formulations evidence lower lipid crystallinity in agreement with the obtained DSC data. From Figure 3, it was clearly shown that no peak of ZTO was detected in drug-loaded NLC (formula D) whereas it is always present in the mixtures. This confirms that ZTO was molecularly dispersed (dissolved) in the lipid phase of NLC.

Drug release behavior

The release behavior in vitro of ZTO-loaded NLC with different Miglyol 812N content was investigated in 1.2% Tween phosphate buffer (pH 7.4) and are shown in Figure 4. Because of the oily and low solubility of ZTO, 1.2% Tween 80 was introduced into the drug release medium to ensure the sink condition. The release profiles of NLCs indicated a biphasic pattern with a burst release during the first 8 hours, followed by a sustained release over 90 hours. The initial fast release of drug from the NLCs could be explained by drug desorption from the outer surface of the NLCs and the larger specific

Table 4. Melting points, enthalpy, and crystallinity of freeze-dried samples.

Samples	Melting points (°C)	Enthalpy (J/g)	Crystallinity (%)
Formula D (ZTO–NLC)	43.17	23.7	16.15
Blank-formula D (NLC)	49.01	48.6	33.13
Blank-formula A (SLA)	52.18	61.8	42.12
Bulk	56.9	146.7	100

surface of the smaller particles increasing the initial drug release rate. After that the drug release of four recipes displayed sustained release, suggesting that the dispersed ZTO can only be released slowly from the lipid matrices through diffusion or the matrix erosion manners, and this resulted in the slow release of the drug in the latter stage[17]. It was observed that the release of ZTO from the SLN (formula A) is lower than that NLC (formulas B, C, and D). This meant that the drug diffusion through the liquid lipid phase was faster than that through the solid lipid phase. The drug releasing rate of lipid nanospheres was enhanced by increasing Miglyol 812N content. When the Miglyol 812N content increased up to 30 wt.%, the particle size significantly decreased (Table 2), consequently, the specific surface area was increased. Therefore, the fastest release rate, emerged in the ZTO–NLC of 30 wt.% Miglyol 812N content, was resulted by both smaller size and higher liquid lipid content.

Pharmacokinetic evaluation

Figure 5 shows the plasma concentration–time profiles of germacrone after administration of ZTO–NLC and ZTO injection to rats at a dose of 100 mg/kg (calculated by ZTO), respectively. The noncompartmental pharmacokinetic parameters in Table 5 were calculated based on the observed plasma levels of germacrone. It can be seen from the calculated pharmacokinetic parameters in Table 5 that there was obvious difference between the parameters of the two drug formulations. The $t_{1/2}$, area under the blood concentration–time curve, mean resident time, and V_{SS} were significantly longer or larger and the CL was lower compared to ZTO–NLC to the ZTO injection ($P < 0.05$), which indicated that with the equidosage, the ZTO–NLC exhibited an obvious prolonged acting time and the ZTO–NLC might enhance ZTO absorption in vivo. The prolonged acting time of ZTO–NLC was largely due to the NLCs protection of the ZTO from recognition and uptake by RES that prolonged the circulation time significantly[28]. More studies are necessary to verify the above speculation and to elucidate the real mechanism of the prolonged acting time of ZTO–NLC. There will also be further research to validate the drug distribution of ZTO–NLC in vivo.

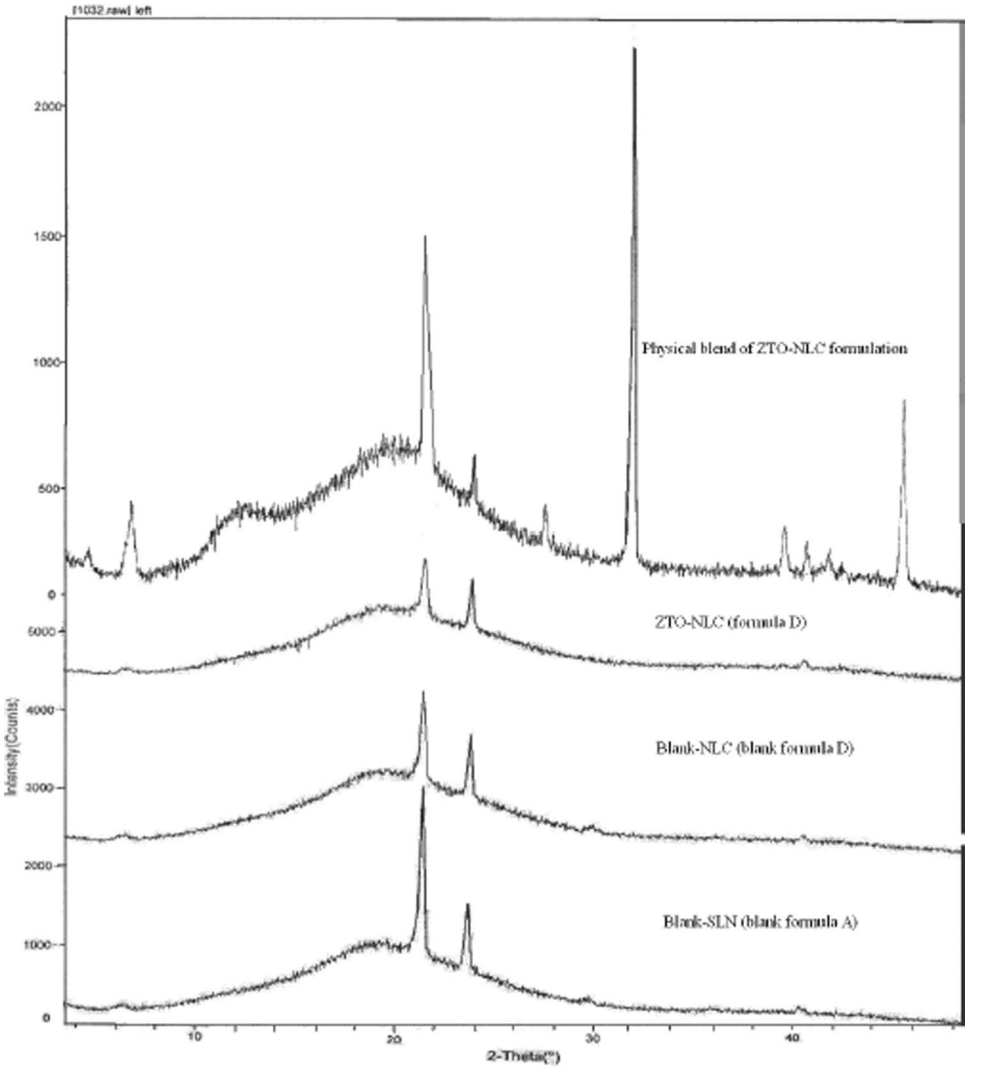

Figure 3. X-ray diffraction patterns of SLN and NLC.

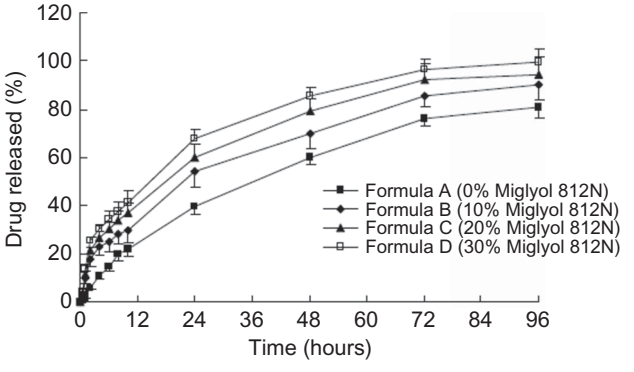

Figure 4. In vitro drug release profiles of lipid nanospheres with different Miglyol 812 content ($n = 3$).

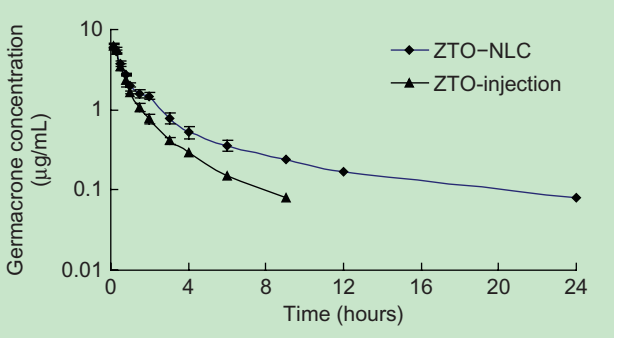

Figure 5. Mean plasma concentration–time profile of germacrone after intravenous administration (100 mg/kg ZTO dose) of ZTO–NLC (♦) and ZTO injection (▲). Each point represents the mean (SD) ($n = 5$).

Table 5. Comparison of pharmacokinetic parameters between ZTO–NLC and ZTO Inj ($n = 5$).

Parameter	ZTO Inj	ZTO–NLC
$t_{1/2}$ (hours)	2.55 ± 1.02	8.88 ± 1.78*
$AUC_{0-\infty}$ (μg·h/mL)	6.25 ± 2.13	11.47 ± 2.04*
MRT (hours)	2.20 ± 0.89	7.73 ± 1.96*
CL (L/h·kg)	1.50 ± 0.65	0.82 ± 0.21*
V_{ss} (L/kg)	3.29 ± 1.34	6.31 ± 1.23*

$t_{1/2}$, biological half-time; AUC, area under the blood concentration–time curve; MRT, mean resident time; CL, clearance; V_{ss}, apparent volume of distribution at steady state.
*Significantly different from the solution ($P \leq 0.05$).

Conclusions

The results of this study show that it is possible to formulate lipid nanoparticles with good properties with mixed lipid consisting of Crodamol SS and Miglyol 812N. The mixed lipid used in this study yielded NLC formulated with Miglyol 812N of lower crystallinity compared with SLN, which is necessary for increased drug loading capacity and drug releasing rate. The evaluation of pharmacokinetics of ZTO–NLC and ZTO injection suggested that the ZTO–NLC lends ZTO the merit of prolonged acting time over the conventional injection. Therefore, it was suggested that this NLC system could be used as a parenteral drug carrier for water-insoluble oily drugs.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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