Pharmacogn. Mag.
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ORIGINAL ARTICLE

Improved Oral Bioavailability of Total Flavonoids of *Dracocephalum moldavica* via Composite Phospholipid Liposomes: Preparation, *in-vitro* Drug Release and Pharmacokinetics in Rats

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Submitted: 28-08-2015 Revised: 16-10-2015 Published: 13-10-2016

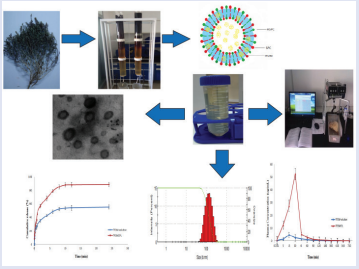
ABSTRACT

Background: *Dracocephalum moldavica* L is a traditional Uygur medicine for centuries, total flavonoids extracted from *Dracocephalum moldavica* are the major active ingredients of herbs, which possesses significant medicinal values to treat coronart disease and hypertension, due to the glycosyl group on the ring, total flavonoids of *Dracocephalum moldavica* has low hydrophilic and poorly absorbed after oral administration, so one way is the formulation of poorly water soluble and permeabledrugs with lipids containing formulations such as Composite phospholipid liposomes to improve the absorption profile of drug. **Objectives:** To prepare composite phospholipid liposome (CPL) encapsulatetotal flavonoids extract from *Dracocephalum moldavica* (TFDM), determine its physicochemical properties,investigate its *in-vitro* release and evaluate the pharmacokinetics in Sprague-Dawley (SD) rats to increase the bioavailability of TFDM-CPL. **Material and Methods:** The TFDMCPL was prepared by the method of ammonium sulfate transmembrane gradients. The CPL and TFDM were separated by Sephadex-G50 chromatography. The concentration of TFDM in the CPL was detected by HPLC, then the entrapment efficiency (EE) was evaluated. And the shape, particle size, zeta potential, drug release *in vitro* of TFDMCPL were investigated, and the pharmacokinetics was evaluated by rat jugular vein intubation tube in SD rats. **Results:** The EE of TFDM was 84.17±2.2%, mean size of TFDMCPL was 136.2±3.7nm, polymey disperse index (PDI) was 0.158±0.015 and zeta potential was -19.8±1.2mV. TFDM-CPLwere found to enhance the release of drugs more effectively than TFDM based on the *in vitro* model and Following oral administration of TFDM, the plasma exposures of TFDM-CPL was significantly extended, and the mean concentration of TFDM-CPL was significantly higher compared to TFDM-solution . TheC_{max}, $t_{1/2}$, $AUC_{0\text{-}12\ h}$ values of TFDM for group of TFDM-CPL were siginificantly increased. **Conclusion:** The method of ammonium sulfate transmembrane gradients is suitable for preparingTFDM-CPL. And TFDM-CPL have potential to be used to improve the bioavailability of poorly soluble drugs after oral administration.

Key words: Total flavonoids extract from Dracocephalum moldavica, composite phospholipid liposome, entrapment efficiency, *in vitro* drug release, Pharmacokinetics

SUMMARY

- For the first time, composite phospholipid liposomes (CPL) containing total flavonoids of Dracocephalum moldavica (TFDM) were developed by method of ammonium sulfate transmembrane gradients.
- The TFDM-CPL was a significant improvement in bioavailability compared to the TFDM-solution, with a 10-fold increase in relative bioavailability *in vivo*.
- The TFDM-CPL was still stable during storage at 4°C for 6 months.



Abbreviations Used: CPL: composite phospholipid liposome.; TFDM: Total Flavonoids Extract from *Dracocephalum moldavica*; SD:Sprague-Dawley; EE:entrapment efficiency; PDI: polymey disperse index; TFDM-CPL: Total flavonoid extract from *Dracocephalum moldavica* – composite phospholipid liposome; DM:*Dracocephalum moldavica* L.; SPC: Soybean phospholipid; HSPC: Hydrogenated soya phosphatide; PBS: phosphate buffered saline; HPLC: high performance liquid chromatography; TEM: transmission electron microscopy; CMC-Na: Carboxy Methyl Cellulose-Natrium; AUC: area under the curve

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DOI: 10.4103/0973-1296.192201

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INTRODUCTION

Dracocephalum moldavica L(DM) is an annual herbin Labiatae family, which is used as a traditional Uygur medicine for centuries in the name of Baeiranjiboya[1]. DM possesses important medicinal values against the following diseases: Bronchitis, hypertension, hepatitis, dizziness, biliary tract infections and other diseases. DM is mainly produced in several provinces of northeast, northwest, and north of China; South eastern Xinjiang has abundant resources.[2] DM has a long history to be recorded in many classical books on Uygur medicines. A portion of

Cite this article as: Zeng C, Jiang W, Tan M, Xing J, He C. Improved oral bioavailability of total flavonoids of *Dracocephalum moldavica* via composite phospholipid liposomes: preparation, in-vitro drug release and pharmacokinetics in rats. Phcog Mag 2016;12:313-8.

minority population in Xinjiang region uses this herb alongside tea, and the civil society uses this as a Uygur medicine to treat coronary heart disease, cold nervous headache, colds, and bronchitis etc., It is also used to improve the quality of blood.[3] Flavonoids are the active ingredients in the DM. Thecurrent study shows that main components of TFDM are tilianin, luteolinglucuronide and rosmarinicacid[4-5] [Figure 1].

TFDM has low solubility and low permeability. So one way is the formulation of poorly water soluble and permeable drugs with lipids containing formulations such as CPL to improve the absorption profile of drug.[6] CPL represent an advanced and versatile nanodelivery system for a wide range of active therapeutics, which were formed by mixtures of different phospholipids(soybeanlecithin, SPC and Hydrogenated soya phosphatide, HSPC).[7] CPL can be prepared to have many useful properties, by varying the type of phospholipid used to make CPL, and by attaching some molecules to the surface of liposomes. They have been used for oral drug delivery to improve the oral bioavailability of some drugs that are not easily absorbed.[8-10]

Till date, neither *in-vitro* drug release nor *in-vitro* investigations have been reported by any studies on the effectiveness of CPL as a delivery system to enhance oral bioavailability of TFDM. So, for the first time, this study was able to successfully prepare TFDM-CPL for oral administration. The *in vivo* pharmcokinetic study of TFDM in SD rats showed an enhanced bioavailability.

MATERIALS AND METHODS

Materials

TFDM (Xinjiang Just Pharmaceutical Company, China); Soybean phospholipid (SPC, purity:96%, lipoid company, German); Hydrogenated soya phosphatide (HSPC, purity:98%, Shanghai Advanced Vehicle Technology Pharmaceutical Ltd, China); Cholesterol (Hui Xing Biochemical Reagent Co. Ltd, China); Tilianin (purity>98%,Xinjiang Pharmaceutical Research Institute); Luteolin glucuronide (purity>98%,Xinjiang Pharmaceutical Research Institute); Rosmarinic acid (purity>98%,Xinjiang Pharmaceutical Research Institute); Sephadex G-50 (Beijing Pharmacia company, China), Other chemicals and reagents used were chromatographic or analytical grade.

Animals

Male SD rats weighing 200-240 g were obtained from Animal Center of XinJiang Medical University (XinJiang, China). The rats were housed in a temperature and humidity controlled room (25°C, 52 % air humidity) with free access to water before the experiment.

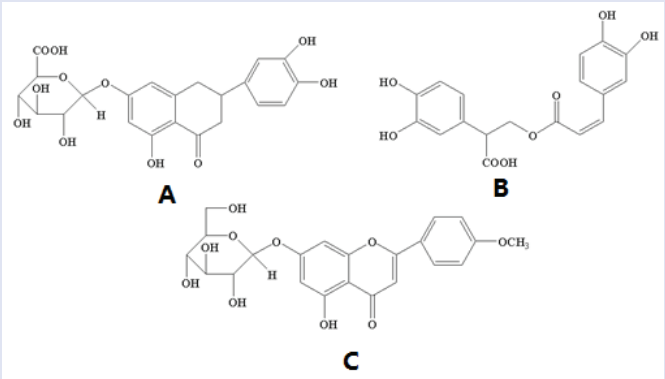

Figure 1: Chemical structures of A:luteolin glucuronide; B:rosmarinic acid; C: tilianin

Preparation of TFDM- CPL

Ammonium sulfate gradient method was used to prepare the CPL of blank. Briefly, SPC, HSPC and Cholesterol were dissolved with the solution of ethanol. The mixture was completely homogenized through using the ultrasound, then was injected into the Ammonium sulfate solution (0.2mol/L) and was stirred for 30 min by magnetic stirrer and reclaimed. The mixture was sonicate for 5 min by probe sonication for 1 min cycles(1 s working and 2 s rest) at 400W. Finally, Theresulting mixture was placed in the dialysis bag (molecular weight cut off 8000-14,000) and the receptor compartment was filled with 10 times Phosphate Buffered Saline (PBS, pH=7.4) of volume for 8h.

Phosphate Buffered Saline (PBS, pH=7.4) contained TFDM(0.2mg /mL) was injected into CPL of blank and was stirred for 20 min by magnetic stirrer. The resulting CPL suspension was extruded through fitration membrane with 0.22 μm pore size.

Characterization of TFDM-CPL

Particle size distribution and the zeta potentials of the CPL were determined by laser diffractonetry using a Malvern NanoZS90. EE was determined by via gel-filtration method with SephadexG-50 column andTFDM (the method of comprehensive score: luteolin glucuronide× 0.3+ rosmarinic acid × 0.3+ tilianin× 0.4) encapsulation was determined following solubilization of vesicles in ethanol and analyzed by a validated HPLC method (r^2 : 0.9998). The quantitative determination of total flavonoids extract from DM was performed using HPLC. The system consisted of a UV detector, C18 column- SPD-10Avp (4.6mm × 250mm, 5μm). The mobile phase consisited of 0.5% methanol(solvent A) and acetonitrile (solvent B)(80:20,v/v). The flow rate was 1 mL/min. The column temperature was kept at 35°C. The detection wavelength was set at 324nm. The 10μL of the controls, TFDM-solution, TFDM-CPL and blank CPL were injected respectively. As shown in [Fig 2], no interferences were found.

Transmission electron microscopy (TEM)

The morphologies of TFDM-CPL and CPL of blank were observed using a transmission electron microscopy (TEM). After dilution with distilled water, the samples were negatively stained with 2% (w/v) phosphotungstic acid for observation.

CPL stability study

Empty CPL and TFDM-CPL(approximately 50 mL) were stored in plastic centrifuge tube (50 mL) at 4°C. in the dark for 6 months. The vesicle mean particle size, PDI and EE were determined at t_0 and after 6 months.

In vitro release of TFDM- CPL

The studies of *in-vitro* release were performed by the dialysis bag method. First of all, the dialysis bag (molecular weight cut off 8000-14,000) was soaked in distilled water for 12 h before use. Then, 10 mL of TFDM or a sample of TFDM-CPL (0.1mg/mL) was placed in the dialysis bag and the receptor compartment was filled with 100 mL of phosphate buffer (pH 7.4) at 37°C with gentle agitation (30 rpm).1.0 mL of the dissolution medium was withdrawn from the receptor compartment at intervals of 1,2,3,4,6,8,10,12,24 h and replaced with the same volume of fresh dialysis medium. Finally, the concentration of TFDM (the method of comprehensive score: luteolin glucuronide× 0.3+rosmarinic acid × 0.3+tilianin× 0.4) was determined by HPLC. All analyses were performed in triplicate to allow proper statistical analysis.

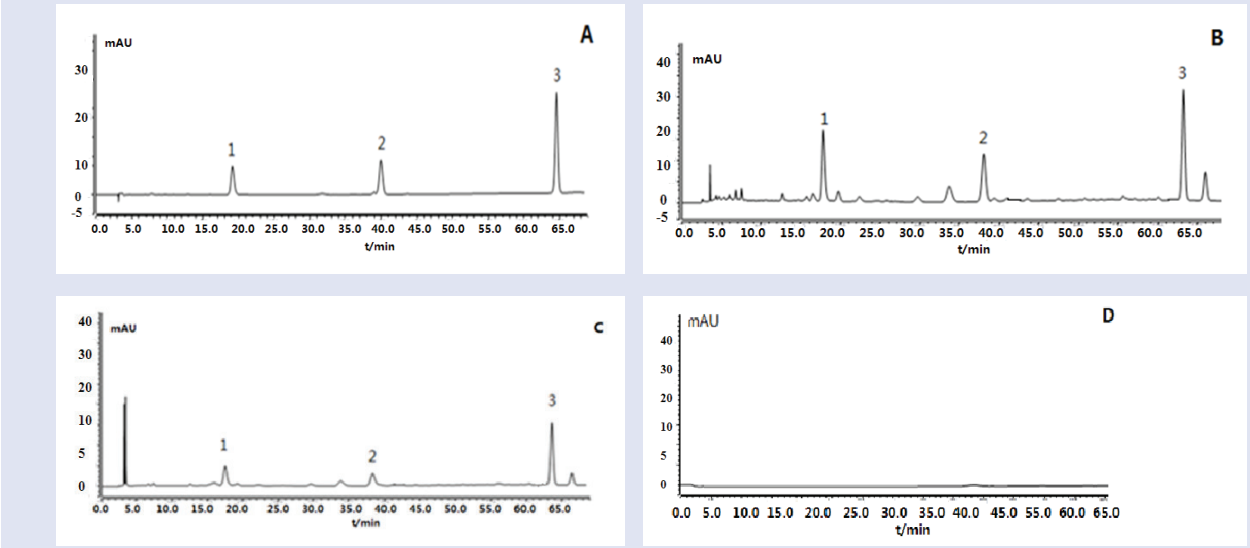

Figure 2: HPLC chromatograms A. controls; B. TFDM-solution; C. TFDMCPL; D. negative controls (CPL of blank); 1. luteolin glucuronide; 2. rosmarinic acid; 3. Tilianin

Oral pharmacokinetics of TFDM-CPL in rats

Date analysis

All the experimental data were expressed as the mean ± SD. The date analysis was performed by Kinetica 4.4.1, and the pharmacokinetic parameters were obtained.

Chromatographic conditions

The HPLC system consisted of an LC-10AT pump and a SPD-10A UV-Vis detector. Chromatographic conditions were as follows: a Shim-pack ODS (4.6mm × 250mm, 5μm) with the column temperature of 35°C; the flow rate was 1 mL/min; detection wavelength was set at 324 nm; the mobile phase consisited of 0.5% methanol and acetonitrile (80:20,*v/v*) and with an injection volume of 20 μL.

Plasma sample preparation

Liquid-liquid extraction was adopted to separate TFDM from plasma samples (rats). First of all, 200 μL of plasma and 2 mL acetonitrile were put into a centrifuge tube. And then, the samples were adequately mixed by vortexing for 3 min and centrifugation at 12,000 rpm for 10 min, 2 mL of supernatamt was put into another clean tube and nitrogen-dried on a 40 °C water bath. The residue was dissolved in 200 μL of acetonitrile and vortexed for 3 min and centrifugation at 12,000 rpm for 10 min. Finally, 20 μL of the resultant mixture(the method of comprehensive score: luteolin glucuronide× 0.3+ rosmarinic acid × 0.3+ tilianin× 0.4) was transferred to an HPLC system for analysis.

In vivo Pharmacokinetic study of DMCPL

SD rats were obtained from the Xinjiang Medical University Laboratory Animal Ltd. and house on standard laboratory diet at an ambient temperature and humidity in air-conditioned chambers and were used for the present studies. All the animals were pathogen free and allowed to access food and water freely. All animal experiments were conducted in full compliance with local, national, ethical and regulatory principles with the approval of the Institutional Animal Care and Use Committee at Xinjiang Medical University.[12]

Male SD rats (220 ± 20 g) were randomly and equally divided into 2 groups. Before the oral administration, all rats were fasted for 12 h, but allowed free access to water. One group of rats was given 300 mg/kg dose of free TFDM suspension (30mg/mL DM, suspended in 0.5 % (w/v) CMC-Na aqueous solution) and the other given the same dose of TFDM-CPL (30mg/mL). The blood samples were collected from the jugular vein at specified intervals (0.01,5,15 min, 0.5,1,2,4,6,8,12 and 24 h after oral administration) (Figure 3). Then the heparinized blood was immediately centrifuged at 3000 rpm for 10 min and treated as described in the "plasma sample preparation" section for further assay.

RESULTS AND DISCUSSION

Drug-loaded CPL mean size, zeta potential and EE

Table 1 presents the mean size and the zeta potential of the CPL suspension with and without TFDM.

The addition of the drug increased slightly the vesicle size and PDI (respectively, 106.4 and 136.2 nm, 0.124 and 0.158 without and with TFDM)(Figure 4).This increase of the mean size could be explained by the entrapment of the total flavonoids extract from DM in the vesicles bilayers.

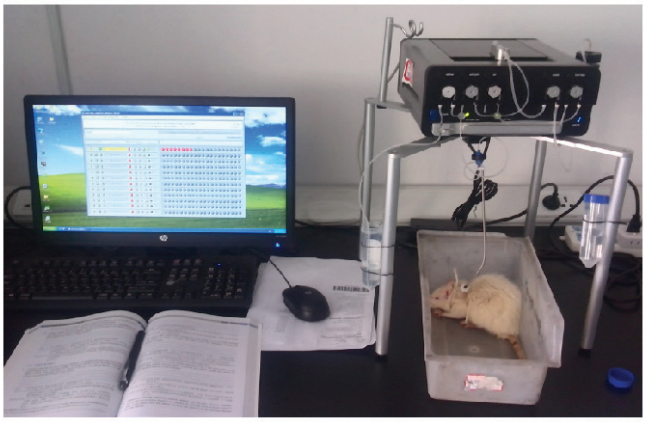

Figure 3: Jugular blood collection in a rat jugular vein cathetherization model (conscious)

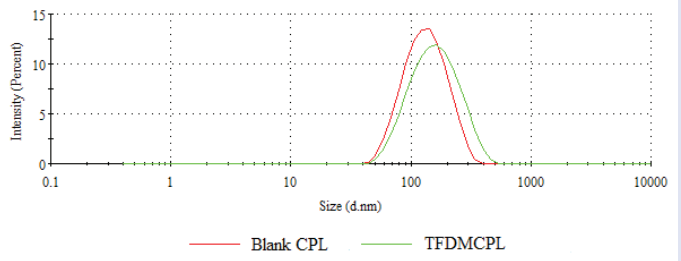

Figure 4: The particle size and PDI of Blank CPL and TFDMCPL

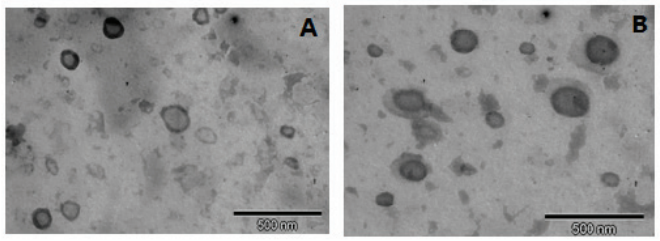

Figure 5: Transmission electron microscope images of morphology of A (Blank CPL) and B (TFDMCPL)

Table 1: The mean size and zeta potential of drug-free and drug-loaded CPL

Batch	Mean size ± SD [a] (nm)	Zeta potential ± SD [a] (mV)
Drug-free CPL [b]	106.4 ± 2.4	-26.7 ± 0.8
Drug-loaded CPL [b]	136.2±3.7	-19.8 ± 1.2

[a] standard deviation (n=3). [b] The mean of 3 batches.

The drug-loaded CPL suspension had an upper zeta potential compared to drug-free formulation. Indeed, the zeta potential was -26.7 mV for the drug-free CPL suspension and became -19.8 mV for the drug-loaded CPL suspension. Zeta potential measurements give information about the surface properties of the carrier and therefore can be useful to determine the type of the association between the active substance and the carrier (whether the drug is encapsulated in the body or simply adsorbed on the surface).

In our study the negative surface charge was further shielded in the presence of the drug, suggesting that at least a part of the association was surface-adsorption and the rest was incorporated within the lipidic matrix.[11] These zeta potential data allowed predicting a very good stability of the preparations (a negative zeta potential higher than 15 mV was sufficient to prevent vesicle coalescence).[12]

The desirable therapeutic effect of CPL as drug carriers can be achieved if they are loaded with a sufficient amount of an active compound. Therefore, suitable entrapment efficiencies of drugs are required. In our study, a relatively higher encapsulation efficacy was found with more than 22% in comparison to traditional liposomes. Thus, the high EE was believed to be due to the high lipophilicity of TFDM and its good solubility in phospholipids.

Surface morphology study by transmission electron microscope(TEM)

As shown in Figure 5, the morphological investigation using transmission electron microscopy revealed nanometric sized and spherical shaped CPL. According to TEM micrographs, CPL ranged in size from 100 to 150 nm correlating well with measurement obtained. Vesicle membranes were composed of phospholipids bilayers.

Stability study of CPL

The mean particle size, PDI of CPL and the EE of TFDM-CPL were examined after 6 months of storage at 4°C. An increase of size of empty CPL from 106.4 ± 2.4 nm to 128.3 ± 5.6 nm and PDI from 0.127 ± 0.012 to 0.167 ± 0.021 and size of TFDM-CPL from 136.2 ± 3.7nm to 186.7 ± 3.7 nm and PDI from 0.158 ±0.015 to 0.205 ± 0.021 were observed. However, the EE of TFDM determined after 6 months of storage at 4°C,were identical to those obtained at t_0 suggesting that CPL retain the TFDM constituent during the storage.

In vitro drug release of TFDM- CPL

To investigate *in vitro* drug release of TFDM-solution and TFDM-CPL, the amount of drug released from CPL was drafted as a function of time. The cumulative amount of TFDM in the receptor over 24 h was charted after administration of TFDM-CPL ,as shown in Figure 6, and the equation matching the results to the release behavior are seen in Table 2. It was obvious that the drug release from CPL lifted significantly. When comparing the results, which were consistent with the general summary, that composite phospholipidliposomal entrapment of drugs promotes their release, and the release behavior of TFDM-CPL, was similar to the one order equation. According to a recent report, CPL, was a novel carrier of nano-formulation delivery system. This could make the drug molecule transported between CPL and cell membranes and might indicate more initial burst release in intestinal tract. Therefore, CPL had a potential application in enhancing the oral bioavailability of TFDM *in vivo*.

Pharmacokinetics studies

The aim of experiment is to evaluate the viability of the CPL as a means of increasing the oral bioavailability of TFDM, the pharmacokinetics of TFDM-CPL was compared with that of TFDM-solution in rats by an HPLC method. The content of TFDM (luteolin glucuronide, rosmarinic acid and tilianin) was more than 82.6%, the content of luteolin glucuronide, rosmarinic acid and tilianin in rat plasma was determined respectively. The method was validated for factors such is linearity, precision, accuracy and stability.

Figure 7 shows the plasma concentration versus time profiles of TFDM-solution and TFDM-CPL. The plasma concentration of TFDM-solution increased with time over the 15 min and decrease slowly up to 12 h and the plasma concentration of TFDM-CPL increased with time over the 30 min and decrease slowly up to 12 h.

Table 3 lists the relevant pharmacokinetic parameters of TFDM-solution

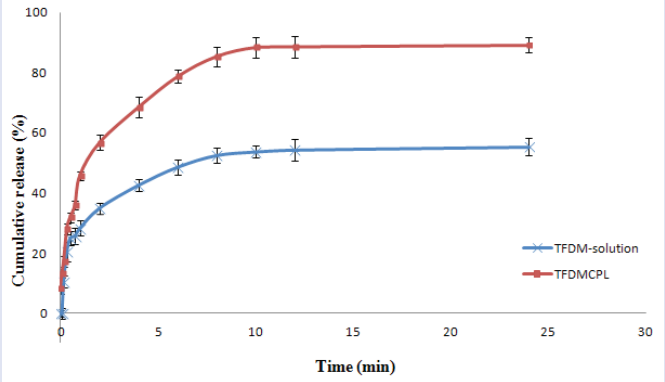

Figure 6: The release of TFDM and TFDMCPL (n=3)

Table 2: Results of release curve fitting

Release	TFDM-solution	r^2	TFDMCPL	r^2
Zero order	Q = 0.3166t+0.0574	0.9249	Q = 0.3568t+0.1139	0.9553
First order	Ln(1-Q) = 0.9214t+0.1123	0.9521	Ln(1-Q) = 0.4996t+0.1112	0.9725
Higuchi	$Q = 0.5861t_{1/2}$+0.1225	0.9342	$Q = 0.3804t_{1/2}$+0.9617	0.9617
Weibull	InIn[1/(1-Q)] = 1.1706Int-0.433	0.9482	InIn[1/(1-Q)] = 0.4405Int-0.637	0.9352

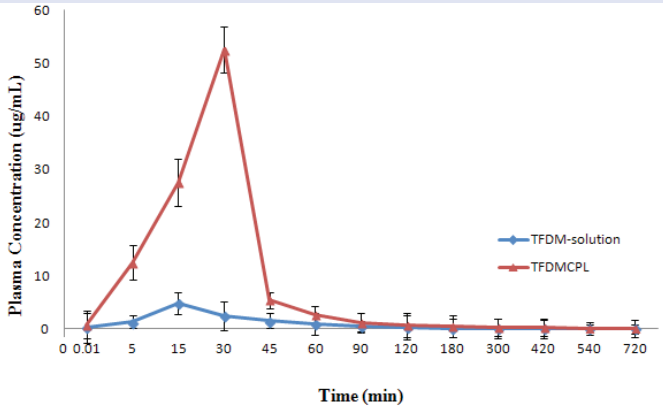

Figure 7: Mean ± SD plasma concentration-time profile of TFDM after oral administration of free TFDM solution and TFDMCPL at 300 mg/kg dose to rats

Table 3: Pharmacokinetic parameters of oral administration of free and formulated drug in rats

Parameter	TFDM-solution	TFDMCPL
C_{max} (ug/mL)	3.73 ± 0.87	51.76 ± 3.22**
T_{max} (min)	16.07 ± 1.24	29.47 ± 3.08*
$t_{1/2}$ (min)	10.95 ± 0.88	13.34 ± 1.34*
$MRT_{(0-\infty)}$ (min)	16.33 ± 0.56	28.19 ± 1.68*
$AUC0-_{12\,h}$ (min ug/mL)	162.79 ± 5.81	1571.92 ± 32.62**
CL (mL/min·kg)	614.27 ± 8.66	63.62 ± 2.23**

Values are expressed as mean ± SD (n= 6) * p< 0.05, compared with TFDM-solution ** p< 0.01, compared with TFDM-solution

and TFDM-CPL.As Table 3 shows, the C_{max}, AUC_{0-12h} and CL of TFDM-solution and TFDM-CPL showed a highly significant difference.

The T_{max} and $t_{1/2}$ extended to 29.47 ± 3.08 min and 13.34 ± 1.34 min ($p < 0.05$), respectively. The C_{max} in TFDM-solution was 3.73 ± 0.87ug/mL, which was different from that in the TFDM-CPL of 51.76 ± 3.22ug/mL ($p< 0.01$). The relative oral bioavailability of the encapsulated TFDM was 965.61 % as compared with the TFDM-solution, which was significantly enhanced ($p<0.01$).Based on research results it has been indicated that the *in-vitro* drug release and rats pharmacokinetics results have a similar variation trends to the oral absorption of TFDM-CPL.

In Fig 7, a pharmacokinetically well defined plasma concentration profile was observed. The liposomal encapsulation provided a great improvement for *in vivo* absorption of TFDM, supporting other studies that used CPL to enhance the bioavailability of poorly water soluble drugs. One of the main reason for improved oral bioavailability might be that CPL could protect drugs from enzymatic metabolism after oral administration.[13] In addition, the majority of drugs stays inside of vesicles of CPL and thus drugs itself may not have a chance to contact esophagus and get higher oral bioavailability.[14] Also, CPL were formed by phospholipid bilayers, resulting in improving the membrane permeability and cellular absorption. Furthermore, biocompatible polymers have been used for surface coating of CPL to extend the residence time in intestine.[15-16] And the addition of cholesterol to the CPL would also enhance stability of CPL *in vivo*.[17] Therefore, the prolonged retention of liposomes in intestine might contribute to increase the drug absorption. In summary, according to our study on the oral administration, the TFDM-CPL led to a significant improvement in bioavailability compared to the TFDM-solution, with almost10-fold increase in relative bioavailability.

CONCLUSION

For the first timeTFDM, which is a poorly water soluble, and low oral bioavailability compounds were successfully encapsulated in the CPL formulations. They encapsulate TFDM constituents with high EE values. According to the physicochemical properties and drug *in-vitro* release of TFDM-CPL, which with high EE, small size, well suited PDI and the final CPL, was able to potentially promote releasing of TFDM.

According to the Pharmacokinetics Studies, TFDM-CPL could be effective to enhance bioavailability of TFDM after oral administration *in vivo*. They were also stable after 6 months of storage at 4°C.Therefore, the novelliposomalnano formulation could be a promising carrier for poorly water soluble drugs and enhanced oral bioavailability of TFDM.

Financial support and sponsorship

This research work was supported by the national natural science foundation of China(81260681).

Conflicts of interest

There are no conflicts of interest

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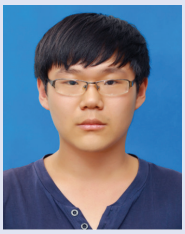
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