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ORIGINAL ARTICLE

Intracellular target delivery of 10-hydroxycamptothecin with solid lipid nanoparticles against multidrug resistance

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Abstract

The main objective of this study was to design a suitable drug delivery system for 10-hydroxycamptothecin (HCPT). In this study, HCPT-loaded solid lipid nanoparticle (HCPT-loaded SLN) was successfully prepared. The HCPT-loaded SLN was characterized by size, entrapment efficiency and drug release manner. The cytotoxicity of HCPT-loaded SLN was assessed *in vitro* using HepG2/HCPT cells and *in vivo* utilizing human tumor xenograft nude mouse model. HCPT-loaded SLN indicated the ability to target HepG2/HCPT cells and accumulated higher drug content in HepG2/HCPT cells. HCPT-loaded SLN enhanced the cytotoxicity of HCPT in a concentration-dependent manner. Based on these results, HCPT-loaded SLN suggested being a promising vehicle for liver-targeted drug delivery. Moreover, it can be of clinical interest to overcome multidrug resistance (MDR) effectively.

Keywords

10-Hydroxycamptothecin, multidrug resistance, solid lipid nanoparticles

History

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Introduction

10-Hydroxycamptothecin (HCPT), a kind of anti-tumor agent, has a strong activity against gastric carcinoma, hepatoma, lung cancer, bladder carcinoma and leukemia [1,2]. It targets the nuclear enzyme topoisomerase I (Top I) and inhibits DNA replication and RNA transcription [3–5], but its clinical therapy is greatly limited by poor solubility, poor tissue specificity, toxic effects to normal tissue, short effect time, high susceptibility to efflux-transporters within tumor cells [2,3,6,7].

Multidrug resistance (MDR) is a major obstacle to successful chemotherapy, which is often the result of over-expression of drug efflux pumps [8,9]. MDR HepG2 cells accumulate a lower intracellular concentration of drug, and the toxicity of chemotherapeutic agents was diminished drastically. Many efforts should have been made to devise a high-performance drug delivery system (DDS) for 10-HCPT with the aim of overcoming the MDR as well as increasing the targeting ability.

Recently, several researches started to investigate the feasibility of solid lipid nanoparticles (SLN) as DDS. SLN are at the forefront of the rapidly developing field of nanomedicine with great potential in clinical. SLN retain some advantages of traditional drug delivery carriers, while circumvent some drawbacks [10,11]. It can enhance the physical stability, protect drug degradation in body, control drug release and decrease the side effect of drug [12,13]. Traditional drug delivery systems discriminately bring cytotoxic agents to body tissues in a highly unpredictable manner. Only a small portion of drugs reach the tumor site, reducing the therapeutic efficacy and increasing systemic drug toxicity [14,15]. SLN could prolong exposure of tumor cells to cytotoxic agents and achieve a passive targeting by enhanced permeability and retention (EPR) [16–19]. The hydrophobic core of SLN provides a storeroom for hydrophobic drug, while the hydrophilic shell conduces to the stability of nanoparticles in aqueous environment [20,21]. What's more, the further modification of surface of SLN may realize the goal of prolonged circulating time and tumor targeting [22–24].

Formulating HCPT in SLN may help to improve bioavailability, enhance the cellular uptake of drug and reverse MDR. Xyloglcan (XG) is a non-toxic, biocompatible and biodegradable natural polysaccharide, which consists of galactose residues, a terminal moiety that can be used to target drug to hepatoma [25–27].

In our research, we used XG as a targeting moiety and developed XG-coated HCPT-loaded SLN. The cytotoxicity effect of HCPT-loaded SLN against MDR HepG2/HCPT cells was investigated *in vitro* and *in vivo*.

Materials and methods

Materials

Xyloglucan was provided by TCI (Shanghai, China) Chemical Industry Development Co., Ltd. 10-HCPT was supplied by

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Hubei Kang Baotai Fine Chemical Co., Ltd (AR, China). Glycerol esters, DMSO and Tween-80 were purchased from Sinopharm Chemical Reagent Co., Ltd (AR, China). All other chemicals were of analytical grade unless otherwise stated. All the organic solvents were purified and dried through common standard methods.

Preparation of solid lipid nanoparticles

Solid lipid nanoparticles (SLN) were prepared according to solvent emulsification-diffusion method. The oil phase and aqueous phase were prepared separately. Oil phase was prepared by dissolving 1 mg HCPT powder in 0.5 mL DMSO, which consisted of 40 mg melted glycerol esters. Twenty microliters of Tween-80 was dissolved into 20 mL 0.01% xyloglucan solution to form the aqueous phase. The oil phase was then dispersed into the aqueous phase. The initial emulsion was kept at 80 °C under magnetic stirring for 24 h to yield HCPT-loaded SLN emulsion.

Characterization of HCPT-loaded SLN

Particle size and zeta potential measurement

The average particle size, polydispersity index (PDI) and Zeta potential of HCPT-loaded SLN were determined by dynamic light scattering (ZEN3690, Malvern Zetasizer NanoSeries, Westborough, MA) at 25 °C.

Drug entrapment efficiency

Four hundred and fifty microliters of chloroform, 4.5 mL methanol and 10 μL acetic acid were sequentially added into 1 mL HCPT-loaded SLN suspension. Then the suspension was subjected to vortex mixing for 2 min and treated with filtration membrane (0.22 μm). HCPT content in supernatant was measured using a high performance liquid chromatography (HPLC, Shimadzu Co., Japan) equipped with a C18 column (Diamonsil TM 150 mm × 4.6 mm, Tianjin, China) at 35 °C, and a UV detector at 384 nm. The mobile phase was composed of acetonitrile and 0.1% triethylamine-PBS buffer solutions (pH 3.0, 25:75, v: v) with a flow rate of 1 mL/min.

The HCPT entrapment efficiency (EE) was calculated as follows:

$$\mathrm{EE} = \frac{\mathrm{A} - \mathrm{B}}{\mathrm{A}} \times 100\%$$

where *A* was the amount of HCPT added in system and *B* was the amount of HCPT in supernatant.

In vitro experiment

HCPT release in vitro

Five milliliters of HCPT-loaded SLN suspension was transferred into dialysis bag, then the dialysis bag (MWCO: 3500, China) was sealed into 250 mL phosphate buffer medium (PBS, pH 7.4, 0.1% sodium azide). The medium was shaking at 37 °C and 100 rpm. At a certain interval time, 1 mL each sample was collected and equivalent fresh PBS of the same temperature was supplemented. Twenty microliters of filtrate was injected into HPLC to quantitatively measure the content of HCPT. Equivalent free HCPT solution was assayed under the same condition as control groups. The cumulative amount of released HCPT was expressed as a percentage of the total drug amount.

Cytotoxicity assay in vitro

HepG2 cells were cultured in RPMI-1640 medium supplemented with 10% (v:v) fetal bovine serum at 37 °C in saturate humidity with 5% CO_2 atmosphere. The drug-resistant HepG2/HCPT cell line was harvested after treatment with 1 ppm HCPT for 3 days. 0.5×10^5 cells/mL MDR HepG2/HCPT cells were seeded at each well and incubated for 24 h under the conditions reported previously. The MDR HepG2/HCPT cells were subjected to gradient concentration of HCPT-loaded SLN or free HCPT solution. After 72 h, 20 μL of 5 mg/mL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to all the wells and incubated for another 4 h. Finally, the medium was removed and 150 mL DMSO was added to each well. After the formazan crystals were solubilized completely, the absorbance was measured by spectrophotometry at 570 nm and the cell viability was calculated as follows:

$$\text{Cell viability} = \frac{\mathrm{B}}{\mathrm{A}} \times 100\%$$

where A is the absorbance of control group and B is the absorbance of treated group.

Measurement of HCPT content in nucleiMDR HepG2/HCPT cells

One milliter of HepG2/HCPT cells suspension (with a density of 1×10^7 cells/mL) was dispersed in 300 mL TM-2 buffer solution (TM-2 buffer solution: 10 mmol/L Tris-HCL, pH 7.4, 2 mmol/L $MgCl_2$, 0.5 mmol/L PMSF). After being incubated for 1 min, the mixture was kept in ice bath for 5 min and then 300 μL 1.0% Triton X-100 was added. After additional 5 min incubation in ice bath, the mixture was passed through filtration membrane (0.22 μm) for six times. The mixture was centrifuged at 800 rpm and 25 °C for 10 min to separate nuclei from cytoplasm. Nuclei were dispersed in 1 mL TM-2 buffer solution. The concentration of HCPT in nuclei and cytoplasm was detected by HPLC method mentioned above.

Measurement of HCPT content in MDR HepG2/HCPT cells

MDR HepG2/HCPT cells were seeded into 96-well plate with a density of 1×10^6 cells/mL. HCPT-loaded SLN and free HCPT solution were respectively added into the 96-well plate after MDR HepG2/HCPT cells grow for 2 h. At a certain interval time, cell-culture medium was refreshed and cells were rinsed by PBS for three times. After ultrasonic extraction for 5 min, 1 mL cell suspension was acidified with 20 μL phosphoric acid and 5 mL ethyl acetate. The mixture was respectively vortex oscillated for 5 min and centrifuged at 3500 rpm for 15 min. The supernatant was dried with liquid nitrogen instrument, and residue was dissolved in 100 μL methanol. Twenty microliters sample was injected to HPLC to be analyzed quantitatively at the same method mentioned above.

In vivo

Specific pathogen-free grade male BALB/c/nu naked mice were fasted overnight before the experiments, but had free access to water. Animals handling and treatments were in accordance with the ''Guidelines for the Care and Use of Laboratory Animals'' published by the National Institute of Health (NIH publication No. 85-23, revised 1985).

Pharmacokinetic study in vivo

Specific pathogen-free grade male BALB/c/nu naked mice were divided into two groups. All mice were respectively tail vein injected with free HCPT solution or HCPT-loaded SLN at a single dose (equivalent dose of HCPT = 2.5 mg/kg). At a certain interval time, 0.5 mL blood sample was collected by retro-orbital venous plexus puncture. Ten microliters of phosphoric acid and 1.5 mL ethyl acetate were doped into plasma samples, and the mixture was respectively subjected to ultrasonic extraction and vortex oscillation for 5 min. The content of HCPT was determined using HPLC at 25 °C with the same method mentioned above.

Antitumor activity in vivo

All specific pathogen-free grade male BALB/c/nu naked mice were divided into three groups and injected with 1 mL HepG2/HCPT cells with an intensity of 10^7 cells/mL at the right axillary region. An obvious tumor could be noticed in most mice 3 weeks later. HCPT-loaded SLN suspension, free HCPT solution (equivalent dose of HCPT = 4 mg/kg) and physiological saline were respectively injected to three groups once a day for a week. At the pre-determined time, the mice were sacrificed, and the tumors were excised. A major axis and a minor axis of tumors were determined by measuring the calipers and tumor volume.

Statistical analyses

All data expressed as means ± SD were representative of at least three different experiments. A value of $p < 0.05$ was considered statistically significant.

Results

Characterization of HCPT-loaded SLN

Dynamic light scattering revealed that HCPT-loaded SLN was 137.5 nm in diameter with a PDI of 0.392 (Figure 1). The loading efficiency was 68.5% and drug content was 3.97 ± 0.38%.

HCPT release *in vitro*

The release rate of HCPT from HCPT-loaded SLN in PBS (pH 7.4) at 37 °C was slower than free HCPT solution (Figure 2). A major problem during the drug release process with free HCPT solution was burst release observed. A prolonged drug release could be obtained by HCPT-loaded SLN. The total amount of released HCPT was approximately 95.87 and 32.58% from free HCPT solution and HCPT-loaded SLN in 12 h, respectively.

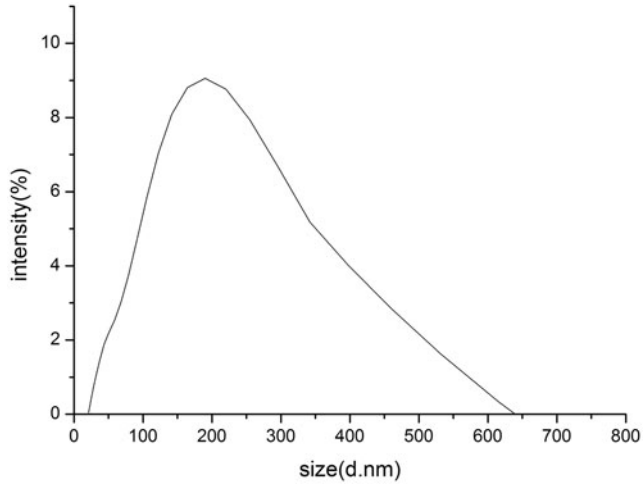

Figure 1. Size distribution of HCPT-loaded SLN detected by DLS.

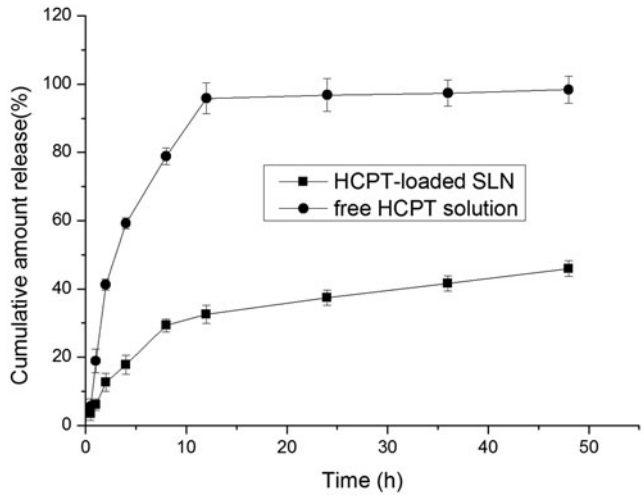

Figure 2. *In vitro* release profiles of HCPT from HCPT-loaded SLN and free HCPT solution. Results are expressed as mean ± SD ($p < 0.05$).

Reverse of drug resistance against HCPT in HepG2/HCPT cells

The cytotoxicity of HCPT-loaded SLN and free HCPT solution against HepG2/HCPT cells were evaluated using MTT assay. Cell cytotoxicity exerted by HCPT-loaded SLN appeared to be much higher than that exerted by free HCPT solution. At the any given same dose, HCPT-loaded SLN generated lower cell viability in comparison with free HCPT solution. An obvious decrease in cell viability in MDR HepG2/HCPT cells was observed in the presence of HCPT-loaded SLN with concentration ranging from 0 to 1.0 ppm. The results indicated that HCPT-loaded SLN reduced the cell growth of MDR HepG2/HCPT cells line in a concentration-dependent manner. At 1 ppm, HCPT-loaded SLN could produce a low cell viability of 13.2%. The cell viability in the presence of free HCPT solution was more than 80%, even at a high drug concentration (1 ppm). The estimated IC50 value of HCPT-loaded SLN was about 0.200 ppm in MDR HepG2/HCPT cells, while that of free HCPT was about 1.420 ppm. These results indicated that enhanced cytotoxicity

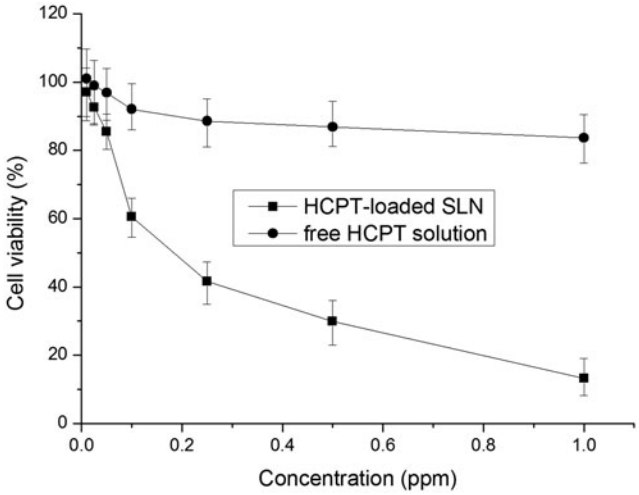

Figure 3. Cytotoxicity *in vitro* of HCPT-loaded SLN and free HCPT solution against the MDR HepG2 Cells. Results are expressed as mean ± SD ($p < 0.05$).

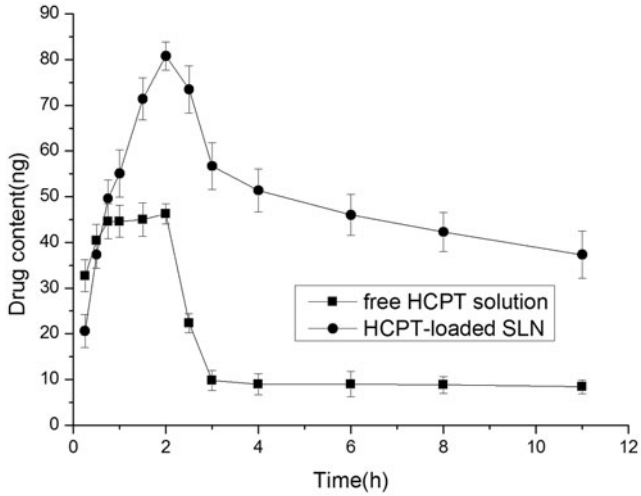

Figure 5. The drug content detected in the nucleus of MDR HepG2 cells. Results are expressed as mean ± SD ($p < 0.05$).

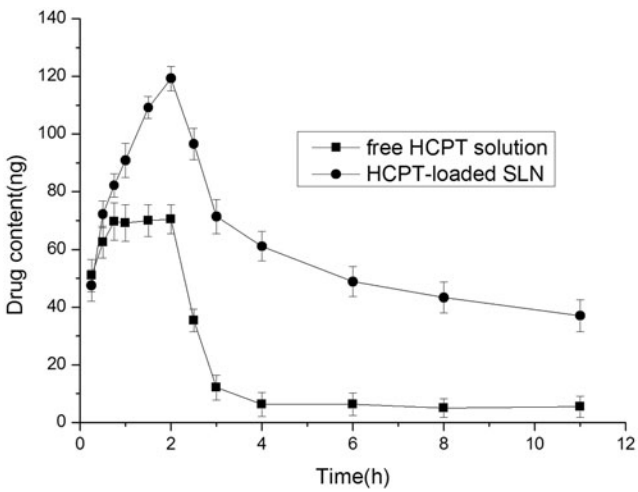

Figure 4. The drug content detected in the whole MDR HepG2 cells. Results are expressed as mean ± SD ($p < 0.05$).

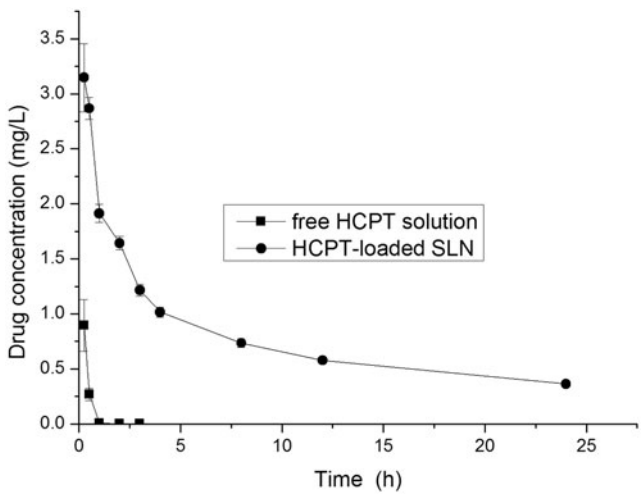

Figure 6. Concentrations of HCPT in plasma excreted by HCPT-loaded SLN, and free HCPT administered i.v. [2.5 (HCPT eq.) mg/kg] in tumor-bearing mice. Results are expressed as mean ± SD ($p < 0.05$).

to MDR HepG2/HCPT cells can be achieved by HCPT-loaded SLN (Figure 3).

Measurement of HCPT content

The drug content–time curves obtained in the whole cells had the same tendency in nucleus. Increasing the drug concentration in the cellular compartment in which the drug exerts its action seemed useful to improve the cytotoxicity of drug. The drug contents detected in the whole cells rapidly reached a C_{max} of 70.5 and 119.3 ng, respectively, for the group treated with HCPT-loaded SLN and free HCPT solution in 2 h. Then, the drug contents detected in the whole cells produced by free HCPT solution rapidly decreased to a trough level of 12.1 ng at in 3 h, while that produced by HCPT-loaded SLN still maintained at a high level of 71.4 ng. At any given time, the HCPT contents generated by HCPT-loaded SLN were higher than generated by free HCPT solution in nuclei, cytoplasm and the whole cells (Figures 4 and 5).

Pharmacokinetics *in vivo*

The plasma concentration against time curves of HCPT was depicted in Figure 6. As shown at each time point in Figure 6, the HCPT plasma concentrations were higher in mice administered with HCPT-loaded SLN than those administered with free HCPT solution. Free HCPT solution in plasma was eliminated rapidly from the circulation in less than 4 h. The plasma concentration in mice administered with HCPT-loaded SLN was maintained at 0.365 mg/L at 24 h post-dose. Pharmacokinetic parameters of HCPT in mice after administrated with HCPT-loaded SLN or free HCPT solution were reported in Table 1. The $T_{1/2}$, AUC and MRT of HCPT-loaded SLN were much higher than that of free HCPT solution. These results showed that the incorporation of HCPT into SLN resulted in an enhanced absorption after *i.v.* administration.

Table 1. Pharmacokinetic parameters of HCPT in mice after i.v. administrations of HCPT-loaded SLN and free HCPT solution at a single dose of 2.5 mg/kg.

Formulation	$T_{1/2}$ (h)	AUC (h mg/L)	MRT (h)
HCPT solution	0.345254	0.222373	0.41495
SLN	14.05083	25.39115	18.74988

Results are expressed as mean ± SD ($p < 0.05$).

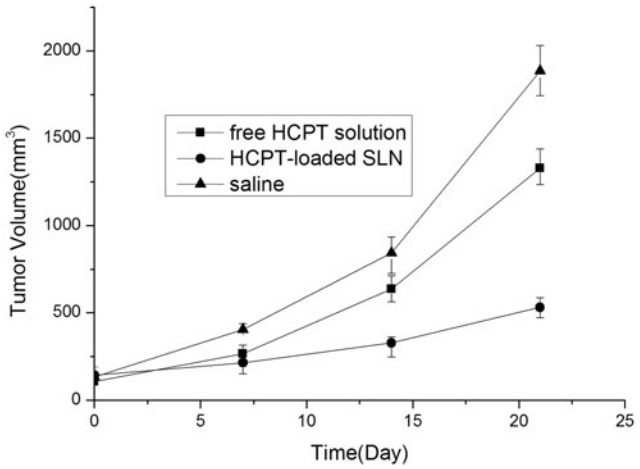

Figure 7. Tumor size changes of the treated xenograft nude mice bearing the drug resistant HepG2 tumors after being injected with HCPT-loaded SLN, and free HCPT solution. Results are expressed as mean ± SD ($p < 0.05$).

Antitumor effect

To further explore whether HCPT-loaded SLN had a superior growth inhibitory effect on the tumor growth *in vivo*, mice with implanted MDR HepG2/HCPT cells were treated with three formulations. Tumor volumes increased rapidly and exponentially when animals were exclusively injected with physiological saline solution exclusively. For the group treated with free HCPT solution and physiological saline, the tumor volumes grew promptly. In contrast, it could be apparently in the group treated with HCPT-loaded SLN, the tumor volume had an obvious smaller size, suggesting the tumor growth was greatly suppressed by HCPT-loaded SLN. Compared with free HCPT solution and physiological saline, HCPT-loaded SLN owned a notably enhanced antitumor efficacy (Figure 7).

Administration of HCPT-loaded SLN caused no mortality at all doses, because that the maximum-tolerated dose (MTD) was over 257.3 mg (HCPT eq.)/kg.

An important indicator of a non-specific toxic effect following treatments with anticancer chemotherapy is body weight decrease. Therefore, the mice body weights following treatments with the HCPT-loaded SLN were monitored. Mice treated with the carriers did not produce any observable side effect and gained weight similar to the control group. Their body weight increased during the course of the treatment.

Discussion

The aim of our study was to design a HCPT-loaded SLN coated by XG with galactose residues for increased antitumor drug effect to HepG2/HCPT cells.

In the MTT assay, HepG2/HCPT cells were more sensitive to HCPT-loaded SLN than to free HCPT solution. Free HCPT solution generated a negligible cytotoxicity to MDR HepG2/HCPT cells. HCPT-loaded SLN was able to slow MDR HepG2/HCPT cells proliferation and showed a better effect on reversing HCPT-resistant MDR HepG2/HCPT cells *in vitro*. To demonstrate the antitumor effect of HCPT-loaded SLN *in vivo*, we developed tumor xenograft nude mouse model. HCPT-loaded SLN exhibited superior antitumor efficacy *in vivo*, which was in full agreement with the cytotoxicity *in vitro*, revealing that the cytotoxicity of HCPT-loaded SLN was significant higher than free HCPT solution.

The mechanisms of enhanced cytotoxicity of HCPT-loaded SLN on HepG2/HCPT cells could be explained by the cellular and subcellular targeting. Nanoparticles are generally captured into the reticuloendothelial system (RES), limiting nanoparticle bioavailability and *in vivo* applications. Strategies that escape the RES clearance and prolong the circulating time of particles seemed necessary to improve the *in vivo* targeting efficiency. Surface modifying the particle characteristics is effective in reducing RES clearance and prolonging their circulation in the bloodstream. In our study, HCPT-loaded SLN was coated with XG. XG is a hydrophilic polysaccharide and has a long lifetime in bloodstream as a vector. The comparative pharmacokinetic parameters of HCPT-loaded SLN and free HCPT solution were reported in Table 1. Based on the comparison of AUC, $T_{1/2}$ and MRT, HCPT-loaded SLN showed significantly higher exposure to HCPT than free HCPT solution. Prolonged blood circulating time and enhanced drug concentration could be achieved by HCPT-loaded SLN.

It is known that tumor is often characteristic of defective, leaky vascular architecture due to poorly regulated nature angiogenesis. The increased cellular concentration of HCPT could be achieved by the long circulation time and EPR. SLN controlled the release of HCPT, prolonged the circulating time of HCPT, and finally accumulated in tumor with the help of enhanced permeability and retention effect (EPR).

The overexpression of receptors on the surface of target tumor cells has been widely explored to enhance the cellular uptake of nanoparticles and minimize side effect. There is abundant ASGPR receptor on HepG2 cells membranes, which has a high affinity for clusters of galactose residues. Due to the galactose residues on XG chain, the XG could be specifically recognized by ASGPR on the surface of on HepG2 cells membranes. Once galactose binds to the ASGPR, the resultant ligand-receptor is rapidly internalized by hepatoma cells. HCPT-loaded SLN coated with XG had a strong affinity to HepG2/HCPT cells and could enter the HepG2/HCPT cells by specific ligand–receptor interactions, increasing intratumoral concentration of cytotoxic antitumor drugs. Therefore, XG coated HCPT-loaded SLN increased the intracellular uptake of HCPT and showed higher antitumor efficacy.

The most effective methods to kill tumor cell is to target drugs specifically to tumor cells, then subsequently deliver drugs to subcellular site within tumor cells, such as nucleus and cytoplasm. HCPT is a well-established topoisomerase I inhibitor, which leads to the death of tumor cells. HCPT need to enter nucleus to exert the antitumor effect maximally.

The drug contents in cell nuclei and the whole cells were measured at pre-determined time points after HepG2/HCPT cells were respectively incubated with the two formulations for 2 h. HCPT-loaded SLN can promote HCPT uptake in the whole HepG2/HCPT cells, especially in the nucleus.

Since cellular internalization routes determine the fate and intracellular distribution of nanoparticles, the development of reliable strategies to influence the nanoparticle cellular internalization pathway can affect therapeutic effect.

In our study, HCPT-loaded SLN have a prolonged circulating time in the presence of hydrophilic XG. Due to the EPR effect, HCPT-loaded SLN can be accumulated in tumor and passive target can be achieved. Moreover, HCPT-loaded SLN can enter Hepatoma cells by the effect of receptor-mediated endocytosis and active target can also be realized. HCPT-loaded SLN could reverse MDR effectively by the effect of EPR in tumor and the mechanism of receptor-mediated endocytosis (RME).

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Declaration of interest

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

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