Body Distribution of Camptothecin Solid Lipid Nanoparticles After Oral Administration

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Purpose. The aim of this study was to investigate the specific changes in body distribution of camptothecin (CA) through incorporation into solid lipid nanoparticles (SLN) by peroral route.

Methods. Camptothecin loaded solid lipid nanoparticles (CA-SLN) coated with poloxamer 188 were produced by high pressure homogenization. The CA-SLN were characterized by transmission electron microscopy and electrophoretic mobility measurement. *In vitro* release characteristics of camptothecin from CA-SLN were studied at different pH media. The concentration of camptothecin in organs was determined using reversed-phase high-performance liquid chromatography with a fluorescence detector after oral administration of CA-SLN and a camptothecin control solution (CA-SOL).

Results. Our results showed that CA-SLN had an average diameter 196.8 nm with Zeta potential of −69.3 mV. The encapsulation efficiency of camptothecin was 99.6%, and *in vitro* drug release was achieved up to a week. There were two peaks in the camptothecin concentration-time curves in plasma and tested organs after oral administration of CA-SLN. The first peak was the result of free drug and the second peak was indicative of gut uptake of CA-SLN after 3 hours. In tested organs, the area under curve (AUC) and mean residence time (MRT) of CA-SLN increased significantly as compared with CA-SOL, and the increase of brain AUC was the highest among all tested organs.

Conclusions. The results indicate SLN could be a promising sustained release and targeting system for camptothecin or other lipophilic antitumor drugs after oral administration.

KEY WORDS: camptothecin; body distribution; drug targeting; solid lipid nanoparticles; sustained release.

INTRODUCTION

Solid lipid matrices used as sustained drug delivery have been well established for many years, e.g. in the form of lipid pellets in commercial products (e.g. Mucosolvan™ Retardkapseln). Solid lipid nanoparticles possess a solid lipid matrix for controlled release of drugs avoiding the burst release as obtained with fat emulsions. Prednisolone loaded SLN showed a prolonged *in vitro* release of up to 5 weeks (1). These nano and microparticles were produced by various techniques (1–4). Lipoid matrices composed of physiological and biodegradable compounds which have lower toxicity compared to synthetic biodegradable polymers (5). Sufficient data are available for the use of drug loaded lipid nano and microparticles for oral delivery. The bioavailability of poorly water soluble drugs can be improved when these drugs encapsulated in lipid-based vehicles via the peroral route (6). The main mechanisms of particulate material across the intestine are uptake via Peyer's patches, intracellular uptake, paracellular passage or a mixed uptake via both routes (7). However, The translocation via the uptake in Peyer's patches seems to be a major pathway after oral administration of nanoparticles.

Camptothecin, a plant alkaloid isolated from *Camptotheca acuminata* (*Nyssaceae*), is the prototype of a novel class of antitumor agents which exert their activities exclusively by inhibition of topoisomerase I (8,9). Topoisomerases are intranuclear enzymes that transiently break and rejoin DNA strands to facilitate processes like replication, recombination, and transcription, essential for cell survival. Camptothecin inhibits the growth of a wide range of experimental tumors. The interaction between camptothecin and topoisomerase I is thought to occur through the attack of a nucleophilic site on the enzyme at the acyl position in the lactone of camptothecin to form a ring-opened species. The lactone functionality appears to play an important role in the biological activity of camptothecin. Unfortunately, lactone is quite labile, and the opening of this lactone at physiological conditions to form the acid salt or carboxylate species resulted in loss of *in vitro* activity and apparently diminished *in vivo* anticancer activity. In acid solution the reverse reaction with the formation of lactone form is favored (Fig. 1). Clinical applications of camptothecin were precluded because of poor water solubility of the lactone form and low biological activity and severe toxicity of carboxylate form. To tackle these problems, several total synthetic or semisynthetic camptothecin analogues were developed and introduced into clinical trial (9). The formulation and the route of application of camptothecin and its analogues have a considerable pharmacokinetic and pharmacodynamic impact (9).

In the present work, we assessed the feasibility of camptothecin loaded SLN to prolong drug release and to achieve *in vivo* specific drug targeting via the oral route. After oral administration, the concentrations of camptothecin in mice were determined in reticuloendothelial cells containing organs as well as in organs containing no reticuloendothelial cells by using reversed-phase high-performance liquid chromatography with a fluorescence detector. The body distribution of free and nanoparticle encapsulated camptothecin was compared.

MATERIALS AND METHODS

Materials

Pure soybean lecithin of medical grade was purchased from Shanghai No.1 Oils and Fats Factory (China). Poloxamer 188 of medical grade was a gift of Surfactant Institute of Jinling Petrochemical Co. Ltd (Nanjing, China). Camptothecin was purchased from Zhejiang Huangyan Pharmaceutical Plant (China). All other chemicals used are either analytical or spectroscopic grade. Double distilled water was filtered through a 0.45 μm (cellulose acetate) membrane before use.

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Preparation of CA-SLN

The stearic acid was added to a pH 8.0 absolute ethanol solution which contained camptothecin and soybean lecithin and adjusted by ammonium hydroxide. The mixture was heated to about 10°C above melting point, and dispersed by sonication (SB3200, Shanghai, China) until the dispersion became nearly clear. The co-emulsifier, poloxamer 188, was dissolved in an aqueous phase containing glycerol as isotonic agent. A predispersion of the melt lipid in this aqueous phase which previously heated to approximately the same temperature as the lipid melt was prepared by magnetic stirring and sonication. This premix was passed through a preheated high-pressure homogenizer (15M-8BA, APV, England) for five cycles at 6000 psi. The hot dispersions were filtered through 0.45 μm filters and allowed to cool down to 4°C quickly to form a CA-SLN suspension, and then were stored at 4°C or lyophilized for storage. The whole manufacture process and storage of CA-SLN were carried out under nitrogen atmosphere.

A typical formulation (w/w%) consisted of camptothecin 0.1, stearic acid 2.0, soybean lecithin 1.5, poloxamer 188 0.5, glycerol 2.25 and double-distilled water to 100.

CA-SOL was prepared by dissolving camptothecin in a mixture of polyethylene glycol 400, propylene glycol and polysorbate 80 (40:58:2).

Particle Size and Zeta Potential

The diameters of CA-SLN were determined by transmission electron microscopy (H-7000, Japan). Samples were prepared by placing a drop of CA-SLN suspension onto a copper grid and air dried, followed by negative staining with a drop of 2 M aqueous solution of sodium phosphotungstate for contrast enhancement. The air-dried samples were then directly examined under the transmission electron microscope. The surface charge of nanoparticles was determined by the electrophoretic mobility of nanoparticles in a U type tube at 20°C.

Determination of Drug Loading and Entrapment Efficiency

The CA-SLN suspension was ultrafiltrated with XHH Hollow Fiber Ultrafiltration membrane (Reili Separation Instrument Factory, Shanghai, China). The concentrations of camptothecin in CA-SLN suspension and the ultrafiltrate were diluted with methanol and assayed by HPLC (10–12).

Drug Release of CA-SLN

In vitro camptothecin release from nanoparticles was evaluated using dialysis bag diffusion technique. Dialysis bags with a molecular weight cut off of 12000 (Sigma) were filled with 500 μl of CA-SLN suspension, and then placed into 500 ml 0.1 M pH 7.4 phosphate buffer saline, pH 5.5 or pH 3.5 distilled water (adjusted by 1.0 M hydrochloric acid). *In vitro* camptothecin release was performed at 37°C using a RC Drug Dissolution Tester (Tianjin Medical Instrumental Factory, Tianjin, China) with the paddle rotation at 50 rpm. Samples were taken from the outer solution, then added with the same volume of fresh dissolution medium each time. The samples were acidified with glacial acetic acid, and diluted with methanol before determination with HPLC.

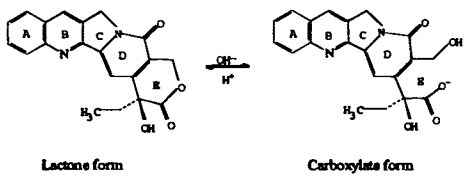

Fig. 1. The structure of camptothecin and equilibrium reaction between the lactone form and the ring-opened carboxylate form.

Body Distribution of CA-SLN

Dosing and Sampling

C57BL/6J mice of a body weight between 17 and 21 g (provided by Central Animal Laboratory of China Pharmaceutical University) were used for investigation. The mice were fasted overnight but had free access to water. CA-SLN suspension and CA-SOL were administered by gavage. For each preparation and each sampling time point, four mice were treated with doses of 3.3 and 1.3 mg CA/kg body weight for CA-SLN and 1.3 mg CA/kg for CA-SOL. At desired time, blood samples were collected from ocular artery through eyeball removal and placed into test tubes containing 10 μl of heparin solution (equivalent to 50 I.U.). The plasma was separated immediately by centrifugation. The animals were dissected and each organ was removed.

HPLC Analysis of Camptothecin

The concentrations of camptothecin were assayed based on the HPLC methods described previously (10–13). The blood and plasma samples immediately mixed with four times of cold methanol (−20°C) and separated by centrifugation after vortex-mixed. The clear supernatant of blood and plasma was immediately chromatograghed to determine the active parent camptothecin. Every organ sample was accurately weighed, homogenized and acidified to pH 3.0 with perchloric acid. The homogenized tissue samples mixed with four times of cold methanol (−20°C) and vortex-mixed for 1 min. After centrifugation, the tissue samples stored at −20°C before total camptothecin concentrations were determined. HPLC analysis was performed using a SP 8800 pump and data get integrator (Spectra Physics Analytical. USA). Separation was achieved on a reversed-phase C-18 column (220 mm × 4.6 mm, 10 μm particle size) with a guard column (ELITE-TEST, USA). A Waters 470 scanning fluorescence detector (Millipore, USA) was optimized according to the peak area of 20 ng/ml standard solution of camptothecin, and camptothecin was monitored using an excitation wavelength 360 nm and an emission wavelength 430 nm with an 18-nm bandwidth. Reversed-phase HPLC was performed with mobile phase composed of 55% (v/v) methanol (spectroscopic grade)-double distilled water (pH 5.5 adjusted with glacial acetic acid) with a flow rate of 1.5 ml/min. For analysis, clear supernatant samples were injected into HPLC system to determine the camptothecin concentration.

Calibration curves were used for conversion of camptothecin peak area to concentration. Appropriate aliquots of standard camptothecin aqueous solutions were added to plasma and the tissue suspensions of mice to provide concentrations ranging

from 7.0 to 180.0 ng/ml. Aliquots of the camptothecin suspension were mixed with 4 volume of methanol and vortex-mixed. Macromolecular components precipitated by methanol were separated by centrifugation. The clear supernatant was immediately chromatograghed. The concentrations of standard camptothecin *versus* peak areas were graphed. The relative and absolute recoveries and reproducibility of the assayed procedure were determined from the calculated drug concentrations in plasma, blood and tissue standards.

Data Analysis. Camptothecin concentrations obtained from mice were pooled to provide mean concentration data. Pharmacokinetic parameters in plasma and organs were obtained from the pooled concentration-time data of each experiment with statistical moment algorithm using PKBP-N1 program package (Nanjing General Hospital of Armed Force, Nanjing, China). The area under the concentration-time curve ($AUC_{0-\infty}$) was calculated using the linear trapezoidal rule, and extrapolated to infinity by dividing the last measurable concentration by elimination rate-constant. The area under the first moment curve ($AUCM_{0-\infty}$) was also calculated using the linear trapezoidal rule. The mean residence time (MRT) was determined by dividing $AUCM_{0-\infty}$ by $AUC_{0-\infty}$. The relative bioavailability (F) were calculated as

$$F = (AUC_{CA\text{-}SLN} \times dose_{CA\text{-}SOL})/(AUC_{CA\text{-}SOL} \times dose_{CA\text{-}SLN})$$

RESULTS AND DISCUSSION

Nanoparticle Characterization

Under transmission electron microscopy, fresh prepared CA-SLN were dense, rigid spheres, and the average diameter (d_{ln}) was 196.8 ± 21.3 nm (n = 3). The surface carried negative charge with Zeta potential of −45.2 ± 5.2 mV (n = 3), which increased to −69.3 ± 2.8 mV (n = 3) after adding sodium citrate as an antifloccutant. Drug loading was as low as 4.8 ± 0.3% (n = 3) and the entrapment efficiency was 99.6 ± 0.3% (n = 3) due to poor water-solubility of camptothecin.

In Vitro Release

In the present experiments, dynamic dialysis was chosen for separation of free drug from nanoparticle-bound drug by dialysis bag. Fig. 2 shows camptothecin release from nanoparticles at different pH dissolution media. The choice of a suitable model for estimation of the drug release from nanoparticles is always problematic. The drug release data from CA-SLN in different pH dissolution media were fitted with Higuchi square root of time equation. The correlation coefficient of the equation was more than 0.95 and $t_{1/2}$ value was longer than 20 h for every dissolution medium. In pH 7.4 phosphate-buffered saline at 37°C, camptothecin lactone opens rapidly to the carboxylate form with a $t_{1/2}$ value of 23.8 min (13). The results showed solid lipid nanoparticles may prevent hydrolysis of camptothecin at pH 7.4 and 37°C.

Body Distribution

A sensitive reversed-phase high performance chromatography with a fluorescence detector was used for the detection

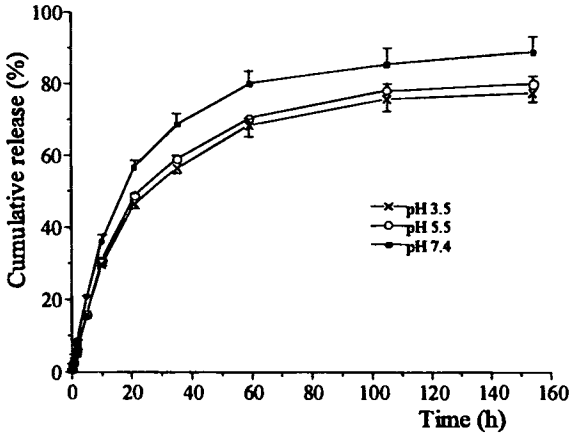

Fig. 2. *In vitro* release of camptothecin from CA-SLN in pH 3.5 (×), pH 5.5 (○) and pH 7.4 (■) dissolution media at 37°C.

and estimation of the time-dependent biodistribution of CA-SOL and CA-SLN at the predetermined time in liver, spleen, kidney, heart, lungs, blood and plasma after oral administration (10–12). The lowest detectable limit of camptothecin was 0.5 ng/ml. The retention time of camptothecin was 5.8 min and every other component was less than 3.0 min. The resolution of camptothecin was always greater than 2.0 and the number of theoretical plates for the HPLC column was maintained at more than 60000 plates/meter during the analytical period. There were no endogenous components that interfered with detection of camptothecin. The absolute and the relative recoveries at low, medium and high concentrations were between 97.0% and 105.0% (n = 6). The standard curves having camptothecin concentrations ranging from 1.4 to 36.0 ng/ml exhibited good linearity, and correlation coefficients over this concentration range were greater than 0.9990 (n = 6) for all measured organs. The assay was accurate and reproducible with coefficients of variation ranging from 1.2% to 5.0% over the concentration range from 1.4 ng/ml to 36.0 ng/ml. In our experiments, the parent lactone camptothecin was determined only in plasma

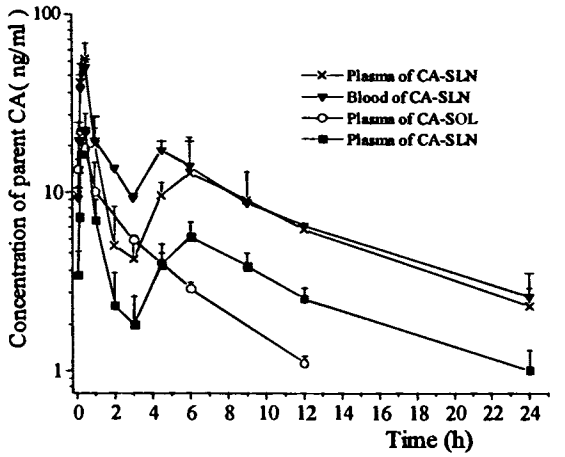

Fig. 3. Parent camptothecin concentration-time profiles following oral administration of CA-SLN with doses of 1.3 (■) and 3.3 (×) mg CA/kg in plasma and 3.3 (▼) mg CA/kg in blood, and CA-SOL with dose of 1.3 (○) mg CA/kg in plasma. Results represent the mean ± SD of four animals.

or blood within 15 min after the blood sample obtained. The total camptothecin in tissue samples was assayed after the samples were acidified to pH 3.0 with perchloric acid to convert the carboxylate form to lactone form since the lactone function is untable and can hydrolyze to carboxylate form at physiological pH (11,12).

There were two peaks in the plasma or blood parent camptothecin level versus time curves of CA-SLN (Fig. 3). Similar phenomena were also found in total camptothecin concentration-time profiles of all measured organs (Fig. 4). The first increase in the camptothecin concentrations between 15–30 min was caused by free and adsorbed drug for the drug absorbed very quickly in the gastrointestinal tract with an absorption half-life of 9.0 min (10). The first plasma maximum concentration of CA-SLN was almost the same as that of CA-SOL, which might be due to that poloxamer 188 could protect camptothecin from hydrolysis in the gastrointestinal tract and blood or the body distribution changes of camptothecin though incorporation into SLN. The second increase in the plasma concentration-time profiles after 3 h might be due to the slow degradation of these nanoparticles in the gut by esterases or translocation of solid lipid nanoparticles across the gastrointestinal tract or the both

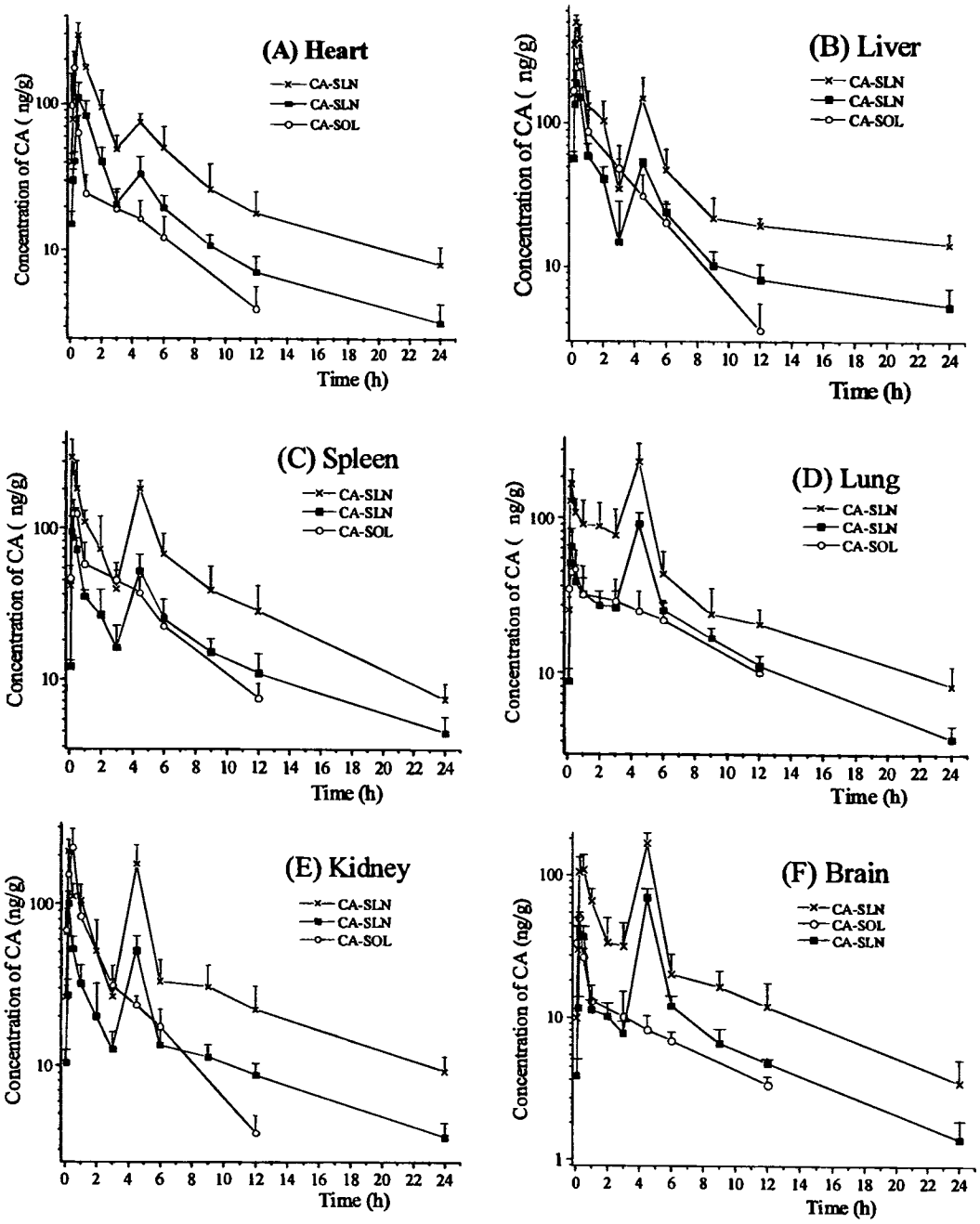

Fig. 4. Total camptothecin concentration-time profiles in organs following oral administration of CA-SLN with doses of 1.3 (■) and 3.3 (×) mg CA/kg and CA-SOL with dose of 1.3 (○) mg CA/kg: (A), heart; (B), liver; (C), spleen; (D), lung; (E), kidney; (F), brain. Results represent the mean ± SD of four animals.

(6,7). *In vitro* degradation of SLN in solutions of pancreatic lipase/colipase showed poloxamer 188 prevented the degradation of particles, owing to the lack of anchoring of lipase to particle surface prerequisite for enzymatic degradation (14). A second increase for ^{14}C-label azidothymidine nanoparticles between 4–8 h (15) and for wax-matrix sustained release ibuprofen microspheres after 8 h was reported (16). The studies carried by Constantinides et al (17) showed the use of medium-chain glycerides and fatty acids/salts in microemulsion formulations to improve intestinal absorption of drugs. Absorption of intact CA-SLN might be existed according to the change of camptothecin concentrations in organs and pharmacokinetic parameters (Table 1) of CA-SLN and CA-SOL, such as higher blood concentration of camptothecin compared to plasma, good targeting of CA-SLN to liver, heart, lung and brain. Speiser (18) disclosed lipid nanopellets as an oral drug-delivery system with a particle size small enough for the transport of intact particles through the intestinal cell layer into the vascular or lymphatic system. The quantity of gut uptake of nanoparticles and their translocation to organs seems strongly to depend on their size (19), hydrophobicity (20), surface charge, bioadhesion of the nanoparticles to the gut (21) and matrix of nanoparticles.

In the reticuloendothelial cell containing organs such as liver, spleen and lung, The $AUC_{0-\infty}$/dose, $AUC_{3-\infty}$/dose and MRT of CA-SLN increased significantly as compared with CA-SOL. The results indicated CA-SLN might be taken up in the gastrointestinal tract and translocated to the reticuloendothelial cell containing organs. The increment of liver MRT was the highest among the tested organs for CA-SLN with dose increase from 1.3 to 3.3 mg CA/kg, indicating that the amount of intact CA-SLN absorbed from gastrointestinal tract might increase and mainly accumulate in liver with the dose increase. The investigation carried by epifluorescence and confocal laser scanning microscopy provided confirmatory evidence for particle absorption within the small intestine and transport to other sites in the body (22). The transport of nanoparticles to liver (15,23), spleen and lymph (24) was also reported after single oral dosing.

The concentration of total camptothecin in brain increased significantly, and F was the highest among the tested organs (Table 1). The high concentration and F maybe result from transporting through the blood-brain barrier by endocytosis of intact CA-SLN and simple diffusion of lactone camptothecin released from CA-SLN. The study of blood-brain barrier transport of lipid microspheres containing clinprost showed that clinprost was transported through blood-brain barrier by simple diffusion of drug released from lipid microspheres and endocytosis of microspheres (25). Fluorescent and electron microscopic studies indicated that the passage of the particle-bound drug occurred by phagocytic uptake of the polysorbate 80-coated nanoparticles by the brain blood vessel endothelial cells. The drug could then be delivered by passive diffusion from the endothelial cells to the brain cells (26). The increase of

Table 1. Pharmacokinetic Parameters of CA-SLN and CA-SOL After Oral Administration

Organ	$AUC_{0-\infty}$ ($ng \cdot h \cdot g^{-1}$)	$AUMC_{0-\infty}$ ($ng \cdot h^2 \cdot g^{-1}$)	$AUC_{3-\infty}$ ($ng \cdot h \cdot g^{-1}$)	MRT (h)	C^1_{max} [a] ($ng \cdot g^{-1}$)	T^1_p [a] (min)	C^2_{max} [b] ($ng \cdot g^{-1}$)	T^2_p [b] (h)	F[c]	F*[d]
CA-SLN (3.3 mg CA/kg body weight; n = 4)										
Plasma	211	2317	159	11.0	56.5	30	12.8	6.0	1.34	0.76
Blood	249	2833	158	11.4	50.6	30	17.3	4.5	1.58	0.64
Heart	1015	9088	628	9.0	292.2	30	75.0	4.5	1.66	0.62
Liver	1652	37287	1166	22.6	495.5	15	147.5	4.5	1.28	0.71
Spleen	1203	9491	897	7.9	290.1	10	181.1	4.5	1.11	0.74
Lung	1168	10742	892	9.2	163.7	15	228.9	4.5	1.27	0.76
Kidney	1019	10434	791	10.2	211.5	15	176.5	4.5	1.10	0.78
Brain	675	4807	516	7.1	108.3	30	168.9	4.5	1.97	0.76
CA-SLN (1.3 mg CA/kg body weight; n = 4)										
Plasma	88	1011	68	11.5	22.1	30	5.6	6.0	1.42	0.77
Heart	421	3673	256	8.7	110.1	30	33.4	4.5	1.75	0.61
Liver	587	8394	392	10.6	190.3	15	52.8	4.5	1.15	0.67
Spleen	472	4975	360	10.5	95.3	10	52.1	4.5	1.10	0.76
Lung	512	4549	416	8.9	65.2	15	92.4	4.5	1.42	0.81
Kidney	375	4036	285	10.8	99.5	15	51.3	4.5	1.02	0.76
Brain	260	1974	216	7.6	38.5	15	70.3	4.5	1.93	0.83
CA-SOL (1.3 mg CA/kg body weight; n = 4)										
Plasma	62	288	31	4.7	21.8	15	—	—	—	0.50
Heart	241	1067	118	4.4	175.3	15	—	—	—	0.49
Liver	510	1410	188	2.8	248.5	30	—	—	—	0.37
Spleen	428	1996	231	4.7	124.4	15	—	—	—	0.54
Lung	361	3009	261	8.3	46.6	30	—	—	—	0.72
Kidney	366	1209	153	3.3	223.2	30	—	—	—	0.42
Brain	135	965	84	7.2	49.7	15	—	—	—	0.62

[a] C^1_{max} and T^1_p are the first maximum concentration and the time to reach the first maximum concentration, respectively.
[b] C^2_{max} and T^2_p are the second maximum concentration and the time to reach the second maximum concentration, respectively.
[c] $F = [AUC_{0-\infty}/dose]_{CA\text{-}SLN}/[AUC_{0-\infty}/dose]_{CA\text{-}SOL}$.
[d] $F^* = [AUC_{3-\infty}]/[AUC_{0-\infty}]$.

concentration and the highest F value of brain indicated CA-SLN had a good targeting effect to brain after oral administration.

It was known that the biological activities of camptothecin and its analogues, both *in vitro* and *in vivo*, are significantly greater for the lactone form than for the carboxylate species. Available data indicated that a closed E-lactone ring is also an important structural requirement for both passive diffusion of drug into cancer cells as well as for successful interaction with the topoisomerase I target (8,9). Camptothecin lactone, however, opened rapidly and completely to the carboxylate form with a $t_{1/2}$ value of 11 min and an almost negligible 0.2% lactone form at equilibrium in pH 7.4 human plasma at 37°C. In whole blood *versus* plasma camptothecin displayed enhanced stability ($t_{1/2}$ value of 22 min and 5.3% lactone at equilibrium) (13). The enhanced stability of camptothecin lactone in human blood was found to be due to drug associations with the lipid biolayers of red blood cells to protect from hydrolysis (27). A wide range of bioactive molecules have been incorporated into sustained release particles to protect them from deactivation in the gastrointestinal tract. Nanoparticles have showed a tendency for drug accumulation in targeting cell for treatment cancers, gene therapy and intracellular infections by bacteria and parasites (28). Because solid lipid nanoparticles might protect camptothecin from hydrolysis in the gut and blood as shown by *in vitro* release in pH 7.4 phosphate buffer saline, cellular uptake of camptothecin might increase as a result of the capture of nanoparticles by an endocytic phagocytic pathway. The stability of camptothecin towards hydrolysis will increase at acidic environment of cell. Solid lipid nanoparticles may be also considered as a good carrier for delivery of camptothecin to cells.

The delayed absorption of CA-SLN in comparison with CA-SOL was coupled with an increase of the F and MRT of camptothecin by more than 10% in tested organs. Similar increase in bioavailability due to entrapment of the drug into nanoparticles was previously reported for azidothymidine (15) and for avarol (29). The Relative bioavailability and MRT values of nifedipine increased significantly with nanoparticles compared to the nifedipine PEG solution (30). The higher bioavailability and longer MRT may be due to an enhanced lymphatic uptake (6,7,18) or the sustained release of camptothecin from CA-SLN.

Camptothecin has severe gastrointestinal and nephric toxicity, myelosuppression and haemorrhagic cystitis (9). After being incorporated into SLN as a sustained release drug delivery system, camptothecin showed lower toxicity, owing to the fate alternation of camptothecin in body, such as the reduce of the camptothecin maximum concentration and the prolongation of T_p (the time to reach the maximum concentration) in kidney. As compared with the CA-SOL, the higher MRT value, plasma parent camptothecin concentrations and AUC in various organs indicated that CA-SLN could much improve camptothecin treatment efficacy.

CONCLUSIONS

This paper shows the interest of SLN as a sustained release and targeting drug delivery system for camptothecin by peroral route. SLN can considerably prolong camptothecin release from CA-SLN and prevent camptothecin from hydrolysis. *In vivo* evaluation revealed that CA-SLN provided higher levels of drug in plasma, blood and tissues for extended period of time than CA-SOL, and the AUC and MRT in all organs increased significantly, especially for brain, blood, heart, lung and liver. SLN present a very promising drug delivery system for camptothecin and for other antitumour drugs in general, and might be advantageous for the drugs that can not cross the blood-brain barrier.

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