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# Enhanced Liver Targeting by Synthesis of $N_1$-Stearyl-5-Fu and Incorporation into Solid Lipid Nanoparticles

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To enhance the liver targeting and reduce the side effects of **5**-fluorouracil (5-Fu), it was acylated by stearyl chloride to obtain $N_1$-stearyl-5-Fu (5-FuS). The chemical structure of the prodrug was confirmed by Nuclear Magnetic Resonance and Infrared Spectrometry. 5-FuS was incorporated into solid lipid nanoparticles (SLN), which were prepared by the physical agglomeration method. The mean diameter of 5-FuS-SLN was 240.19 nm and the drug loading was 20.53%. The release characteristics *in vitro* of 5-FuS-SLN were fitted to the first-order pharmacokinetic model. Compared with 5-Fu injection, a study on the distribution of 5-FuS-SLN in mice showed that 5-FuS-SLN could double 5-Fu concentration in mice livers. The main pharmacokinetic parameters of 5-FuS-SLN in rabbits is shown as follows: $V_d$=0.04336L/kg, $T_{1/2}$ β=1.2834h, CL=0.1632 L/h. In conclusion, 5-FuS-SLN has significant liver targeting properties. The employment of a prodrug to enhance drug liposoluble properties and the preparation method presented in this paper, seem to be an alternative strategy to the traditional colloidal delivery system.

**Key words:** 5-Fluorouracil (5-Fu), Prodrug, Solid lipid nanoparticles (SLN), Targeted drug delivery system

## INTRODUCTION

Drug delivery systems using colloidal particulate carriers, such as liposomes and niosomes, have distinct advantages over conventional dosage forms because the particles can act as drug containing reservoirs. Also, modification of the particle composition or surface can adjust the drug release rate and/or the affinity to the target site (New, 1990). However, besides some problems associated with industrial production, there still remain some significant problems which can not be avoided in the general application of liposomes or niosomes, such as drug incorporation and leakage from the carrier and insufficient shelf stability (Vaizoglu and Speiser, 1986).

SLN is an attractive alternative carrier system to polymeric nanoparticles attracting increasing attention from different research groups (Müller *et al.*, 1995). SLN combines the advantages of polymeric nanoparticles, emulsions and liposomes and avoids some of their major disadvantages. Proposed advantages include: possibility of controlled drug release and drug targeting, increased drug stability, high drug payload, no biotoxicity of the carriers, avoidance of organic solvents and no problems with respect to large scale production and sterilization.

For more than four decades the antineoplastic agent 5-fluorouracil (5-Fu), has been widely used in the therapy of different solid tumor types such as, cancers of the stomach, liver, intestine and so on. Because of the short plasma half-life of 10-20 min, high doses, e.g. 400-600 mg/m$^2$ have to be administered weekly, to reach a therapeutic drug level (Peters *et al.*, 1993). However, 5-Fu may cause the following adverse effects: bone marrow depression, gastrointestinal tract reaction, or even leukopenia and thrombocytopenia. In this context, the use of SLN could be a useful approach to concentrate the loaded drug on the focus of the disease. This would result in an increase in the therapeutic index of the loaded molecule by reducing both the given dose and the side effects.

5-Fu has poor liposoluble properties and it dissolves readily in aqueous media. Synthesis of a more lipophilic

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prodrug is an effective method for lipophobic drugs to form stable SLN (Wang *et al.*, 2002). The purpose of the present study was to obtain stable SLN through combination of 5-Fu with a long chain fatty acid, which is a physiologically acceptable and biodegradable excipient. After i.v. injection of 5-Fu-SLN, it was easily uptaken by organs containing reticuloendothelial cells, especially in the liver. In order to improve the efficiency of 5-Fu for treating liver cancer, 5-Fu-SLN is a promising drug targeting system and may also allow a reduction in drug dosage and a decrease in systemic toxicity.

## MATERIALS AND METHODS

### Materials

Stearic acid and 5-Fu injection were purchased from Chengdu Medicine Company (Chengdu, China). The powdered 5-Fu was a gift from the Drug Research Institute of Chengdu Command General Hospital. The reference standard of 5-Fu was obtained from the Institute of China for Drug Control. All the other chemicals and reagents used were of analytical purity grade, obtained commercially.

Kunming mice, body weight between 18 and 22 g, female or male, and male Japanese rabbits weighing between 1.5 and 2.0 kg, were all provided by the West China Laboratory Animal Center of Sichuan University.

### Synthesis of 5-FuS

According to Robins method (Robins and Hatfield, 1982), the targeting compound was obtained by acylating 5-Fu hexamethyldisilazanized (see Scheme 1).

Seven mililiter of hexamethyldisilazane (HMDZ) and 2 dr. trimethylchlorosilane (TMS) were added to a dried flask with 5-Fu 0.26 g (2 mmol). The reaction mixture was stirred for 4 h at 110°C-120°C, and excess HMDZ was removed by evaporation under reduced pressure. A colorless transparent liquid was obtained. To this liquid, 12 mL of acetonitrile, dried by $CaH_2$, and 0.6 g (2 mmol) stearyl chloride were added; the mixture was stirred for 4 h at approximate 80°C. A portion of solid crystallized from the resulting liquid after putting in room temperature for 6 h. Then the solid was recrystallized from benzene and 0.62 g (yield 78.2%) of white crystals of 5-FuS were obtained.

### Stability of 5-FuS in physiological saline

25 mg of 5-FuS powder was accurately weighed and put into each of three 100 mL triangle flasks, in which physiological saline was added to 100 mL respectively. These suspensions were shaken at 37°C in a water bath for 6 h. At predetermined time intervals, equal volumes (10 μL) of these suspensions were withdraw to determine the 5-Fu concentrations by the HPLC method.

### Stability of 5-FuS in different pH solutions

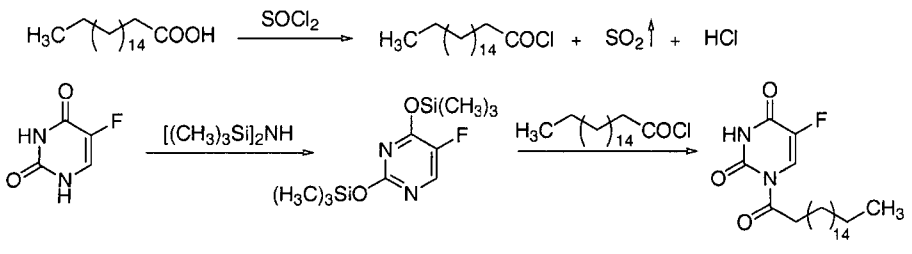
Accurately weighed 5-FuS (about 50 mg) was dissolved in 10 mL tetrahydrofuran (THF) and diluted with water to 90 mL. The solution was then divided into nine equal portions. The pH values of these portions were adjusted, having pH values of 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 9.0 and 10.0, respectively, by 0.1 N sodium hydroxide or hydrochloride acid, and then diluted with water to 10 mL. Each solution was placed at room temperature (25°C) and the concentrations of 5-FuS at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 h were determined by the HPLC method.

### Preparation of 5-FuS-SLN

A physical agglomeration method was employed to prepare a 5-FuS-SLN colloidal solution and the procedure was optimized by a univariate approach. The optimized preparation process was as follows: acetic acid sodium acetate buffer (pH 4.0) was added rapidly to a 4 mL THF solution of 5-FuS 1.0 g and phosphatide 0.6 g with continuous stirring, then the colloidal solution was dispersed in an ultrasonic bath for 10 minutes. The resulting solution was filtered through a $G_3$ filter and a milky 5-FuS-SLN colloidal solution was obtained. 5% mannitol, as a freeze-dried protective, was added to the 5-FuS colloidal solution. The solution was lyophilized for 36 h to obtain 5-FuS-SLN freeze-dried injections.

### Morphology and particle size

The 5-FuS-SLN was examined by transmission electron microscopy (JEM-100SX, Japan). Samples were prepared by placing a drop of the 5-FuS-SLN suspension onto a copper grid and air-drying, followed by negative staining




**Scheme 1.** The synthesis route of 5-FuS

with a drop of 2% aqueous solution of uranyl acetate for contrast enhancement. The air-dried samples were then directly examined under the transmission microscope. The particle size of 5-FuS-SLN was determined by a laser particle analyzer (Master 2000, Malvern).

### Drug release from the 5-FuS-SLN freeze-dried injection *in vitro*

An accurately weighed portion of 5-FuS-SLN lyophilized powder was dispersed in physiological saline and transferred into a dialysis bag suspended in a conical container containing 100 mL physiological saline solution. The container was shaken constantly at 37°C±1°C in a water bath. Samples were withdrawn at predetermined times and the concentrations of 5-FuS were simultaneously determined by HPLC. The quantity of 5-FuS was calculated equivalent to 5-Fu, then the accumulative drug release percentage (Q), was calculated.

### Study on the distribution of 5-FuS-SLN freeze-dried injection in mice

An HPLC assay method was established for determination of the concentrations of 5-Fu in plasma or tissue. The LC-10A high performance liquid chromatography system was used. A CLC-ODS (5 μm, 150 mm×4.6 mm, I.D., Shimpack) column was employed and the guard column was YWG-ODS (10 μm, 10 mm×4.6 mm, I.D.). The mobile phase was methanol: water (1:3 or 1:4). The ultraviolet detector was operated at 265 nm. The analysis was performed at a temperature of 30°C and a flow rate of 1 mL per minute.

Extraction procedures was carry out as follow: An amount of water, double the weight of the tissue, was added to all tissues of mice, which were then well homogenized. 0.5 mL of homogenized plasma or tissue sample was then taken and mixed 1:1 with acetidine containing 100 μg/mL 5-bromouracil as an internal standard, and then a further 7 mL of acetidine was added and mixed with a vortex mixer for 2 minutes. The resulting samples were centrifuged at the rate of 15000 r/min for 10 minutes to separate the two phases. The organic phase was then evaporated to dryness under a nitrogen stream in a 50°C water bath. The residue was redissolved in 0.1 mL of mobile phase. Aliquots of 10 μL were then injected into the chromatograph. A standard curve was prepared according to the chromatographic conditions.

The 5-FuS-SLN freeze-dried powder was dissolved in water for injection, to be used as test solutions. Ninety Kunming mice were randomly divided into groups of 5-FuS-SLN and 5-Fu injection, forty-five in each group. Each mouse was intravenously given 5-FuS-SLN or 5-Fu at a dose of 25 mg/kg body weight corresponding to 5-Fu. The mice were killed in order to obtain the heart, liver, spleen, lung and kidney specimens at 5, 15, 30 min and 1, 2, 4, 8, 12 and 24 h after drug administration. The amounts of 5-Fu in various samples of mice tissue were determined according to the sample preparation and determination method mentioned above.

### Pharmacokinetic study of 5-FuS-SLN in rabbits

The methods of sample preparation and drug concentration determination were the same as that of the distribution study, except for the mobile phase of chromatographic conditions, which was acetonitrile: water (30:70). To prepare a standard curve, different volumes of 5-Fu standard stocks were accurately added into a series of plasma solutions and then the concentrations of 5-Fu in plasma were determined. The regression equation was A=0.00754+0.08295C (r=0.9999). The concentration limits were within 0.1 μg/mL-60 μg/mL. The method was sensitive enough to measure a drug concentration level of 100 ng/mL.

Ten white Japanese rabbits were randomly divided into 5-FuS-SLN and 5-Fu injection groups, five in each group. Each rabbit was intravenously given 5-FuS-SLN or 5-Fu in one ear at a dose corresponding to 5-Fu 25 mg/kg body weight. Two militer blood was taken from the other ear at different times after drug administration, and the 5-Fu plasma concentration was detected by the HPLC method.

## RESULTS AND DISCUSSION

### Structural determination of 5-FuS

5-FuS is a white needle crystal, mp 100-102°C, UV $\lambda_{max}^{MeOH}$ nm: 273, IR (KBr) $cm^{-1}$: 3200, 3100, 2920, 2880, 1780, 1730, 1690, 1486, 1350, 1280. $^1$H-NMR (200-400 MHz, $CDCl_3$) ppm: 9.635 (1H, s, 1), 8.292 (1H, d, $^3J_{H\text{-}F}$ = 6.5 Hz, 2), 3.106 (2H, t, $J$ = 7.2 Hz, 3), 1.670 (2H, m, 4), 1.242 (28H, m, 5), 0.8676 (3H, t, $J$ = 6.4 Hz, 6). All results correspond to the structure of $N_1$-stearyl-5-Fu. The molecular formula is $C_{22}H_3FN_2O_3$ and the molecular weight is 396.08. The structural formula is shown in Fig. 1. Silylanization of carbonyls resulted in a much bigger enhancement of the steric hindrance of $N_3$- than that of $N_1$-. Therefore, a sole acylated product was obtained due to increased selectivity of the $N_1$- acylation. 5-FuS increased the lipid-soluble property of 5-Fu.

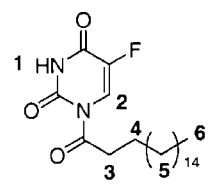



**Fig. 1.** Chemical structure of 5-FuS (This numbering is for the $^1$H-NMR)

### Stability

The hydrolysis of 5-FuS in physiological saline solution was fitted to a zero-order kinetic equation. The plot of the natural logarithm of 5-FuS concentration, determined different pH value solutions, against time, was a straight line with the equation: Y=0.657+1.408C (r=0.989). The pH-rate figure (Fig. 2) was drawn by the reaction rate constant calculated at different pH conditions. It showed that the stability of 5-FuS was greatly affected by pH values. It was found that 5-FuS was much more stable in alkaline solutions than in acid solutions with the minimum pH value [$(pH)_m$] of the hydrolysis rate about pH 4.

### Nanoparticle characterization

Transmission electron microscopy demonstrated a regular spherical surface for 5-FuS-SLN (Fig. 3). The average diameter of 5-FuS-SLN in colloidal solution and its freeze-dried powder were 240.19 nm and 253.63 nm, respectively. The drug loading determined by HPLC was 20.53%. A clear advantage of 5-FuS-SLN is the fact that the lipid matrix is made from physiological lipids and no other emulsifier is added into the formulation, which decreases the danger of acute and chronic toxicity.

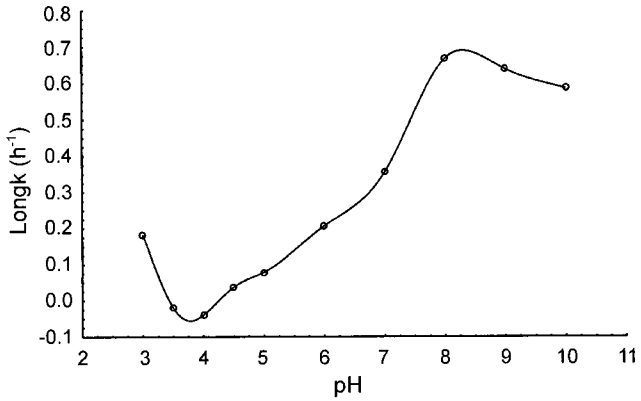



**Fig. 2.** The degradation rate of 5-FuS in different pH solution

**Fig. 3.** Electronic micrographs (×20000). 5-FuS-SLN prepared by the method described above was negative-stained using 1% uranyl acetate and was examined by transmission electro microscopy

### Drug release characteristics *in vitro*

Fig. 4 showed that the drug release curve *in vitro* corresponded to a first-order kinetic equation. The equation was Q=0.0082+0.01787t (r=0.9992). The profile demonstrated that 5-FuS-SLN could prolong the drug release without initial high concentrations. It is difficult for the hydrophobic components to separate from the SLN and diffuse into the water phase, so the drug release was mostly dependent on the hydrolysis of 5-FuS, which first happened at the interface of SLN and water. The 5-FuS in the core of SLN was then hydrolyzed over time.

### Distribution in mice

The results of experimental methodology showed that control plasma caused no disturbance to samples for measurement. The recovery and accuracy of the test is shown in Table I. The freeze-dried injection formulation of 5-FuS-SLN significantly changed 5-Fu distribution *in vivo* (Table II and Table III). During the extraction procedure, 5-FuS was completed hydrolyzed into 5-Fu. Therefore, the

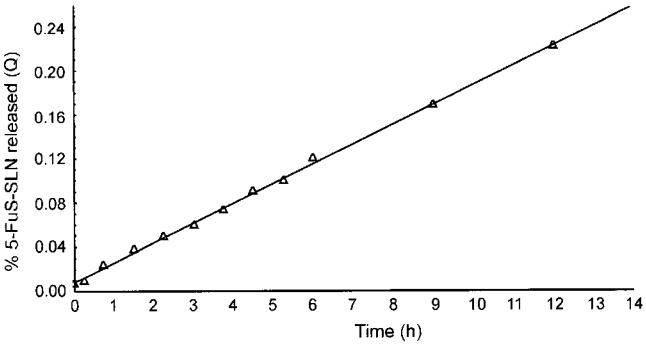



**Fig. 4.** The release *in vitro* of 5-FuS-SLN at 37°C±1°C in physiological saline solution

**Table I.** The recovery rate of 5-Fu from mouse tissue homogenates (Mean±SD, n=3)

| Sample | Added 5-Fu concentration (μg/mL) | | | |
|---|---|---|---|---|
| | 4.0 | 20.0 | 35.0 | 70.0 |
| plasma | 101.37±1.51 | 99.88±1.21 | 101.09±1.90 | |
| heart | 99.04±2.22 | 99.16±0.68 | 98.29±1.27 | |
| spleen | 101.63±0.90 | 98.42±0.69 | 98.41±0.93 | |
| Liver | 100.69±2.29 | | 101.31±1.58 | 97.67±0.85 |
| Lung | 101.04±1.83 | | 101.73±1.70 | 98.77±1.71 |
| kidney | 100.79±2.16 | | 97.55±1.34 | 99.52±2.11 |

**Table II.** Concentration of 5-Fu in plasma and tissues after i.v. administration of 5-FuS-SLN freeze-dried injection in mice (Mean±SD, n=5; μg/mL or μg/g)

| Time (h) | Plasma | Lung | Liver | Spleen | Heart | Kidney |
|---|---|---|---|---|---|---|
| 0.083 | 5.06±0.52 | 40.14±2.59 | 154.10±8.56 | 25.48±1.56 | 21.92±3.14 | 0.04±0.01 |
| 0.25 | 3.23±0.41 | 16.32±2.14 | 52.72±4.91 | 29.69±1.28 | 17.11±2.30 | 0.73±0.03 |
| 0.5 | 1.21±0.15 | 17.28±1.56 | 43.59±2.46 | 14.31±0.98 | 20.10±1.05 | 0.62±0.04 |
| 1.0 | 1.07±0.08 | 23.59±1.36 | 37.47±2.13 | 6.50±0.87 | 17.66±1.39 | 52.56±3.58 |
| 2.0 | 0.43±0.06 | 7.32±0.28 | 29.42±2.83 | 5.70±0.09 | 16.97±0.86 | 58.78±4.66 |
| 4.0 | 0.33±0.05 | 1.79±0.05 | 26.15±1.59 | 5.98±0.34 | 11.96±0.78 | 46.63±4.26 |
| 8.0 | 0.19±0.03 | 1.83±0.04 | 2.36±0.06 | 4.31±0.21 | 10.70±1.18 | 43.72±2.35 |
| 12.0 | 0.12±0.01 | 1.97±0.09 | 2.48±0.11 | 3.00±0.35 | 11.35±1.33 | 24.05±2.01 |
| 24.0 | n.d. | 0.49±0.04 | 1.88±0.23 | 2.87±0.34 | 4.21±0.36 | 17.61±2.30 |

n.d. = not detectable

**Table III.** Concentration of 5-Fu in plasma and tissues after i.v. administration of 5-Fu injection in mice (Mean±SD, n=5; μg/mL or μg/g)

| Time (h) | Plasma | Lung | Liver | Spleen | Heart | Kidney |
|---|---|---|---|---|---|---|
| 0.083 | 29.48±2.03 | 2.59±0.06 | 32.21±2.13 | 22.02±1.44 | 24.27±2.03 | 28.62±2.34 |
| 0.25 | 8.49±1.02 | 3.14±0.04 | 65.65±8.21 | 15.22±1.54 | 6.86±0.45 | 7.06±0.75 |
| 0.5 | 1.25±0.03 | 5.44±0.06 | 1.93±1.56 | 7.52±0.66 | 2.52±0.22 | 4.56±0.23 |
| 1.0 | 0.83±0.04 | 7.32±0.75 | 2.36±0.11 | 8.97±1.04 | 2.18±0.31 | 4.03±0.21 |
| 2.0 | 0.36±0.02 | 101.15±6.59 | 2.39±0.09 | 4.89±0.26 | 0.87±0.07 | 1.93±0.22 |
| 4.0 | 0.25±0.01 | 56.48±4.37 | 1.69±0.24 | 5.97±0.31 | 1.85±0.06 | 2.32±0.16 |
| 8.0 | n.d. | 4.76±0.56 | 1.85±0.08 | 3.15±0.43 | 5.24±0.19 | 2.14±0.14 |
| 12.0 | n.d. | 2.26±0.07 | 2.39±0.13 | 4.05±0.33 | 2.86±0.17 | 1.93±0.24 |
| 24.0 | n.d. | 1.78±0.05 | 1.85±0.18 | 2.74±0.15 | 1.99±0.23 | 1.62±0.08 |

n.d.=not detectable

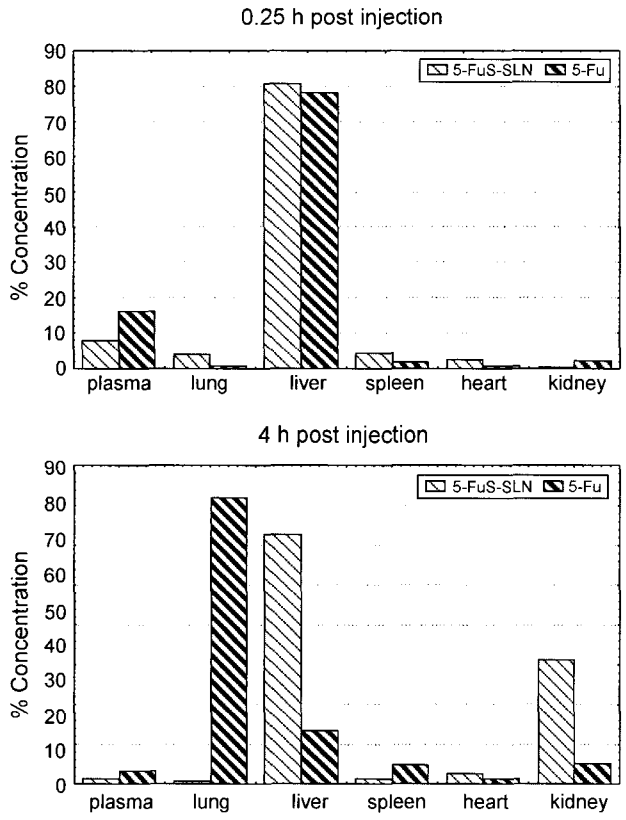



**Fig. 5.** Percent concentration of 5-Fu in different organs and plasma for free 5-Fu injection and 5-FuS-SLN freeze-dried injection.

tissue distribution of 5-FuS-SLN was calculated based on the concentration of 5-Fu. The drug distribution study indicated that, following i.v. administration of 5-FuS-SLN, the 5-FuS-SLN was rapidly eliminated from the circulating blood and mostly recovered from the liver. The drug concentration in the plasma of the 5-FuS-SLN study group was relatively lower than that of the 5-Fu injection study group. In tested organs, about 70% of the amount of the drug was concentrated in liver (Figs. 5, 6). The mean drug concentration in the livers of the 5-FuS-SLN

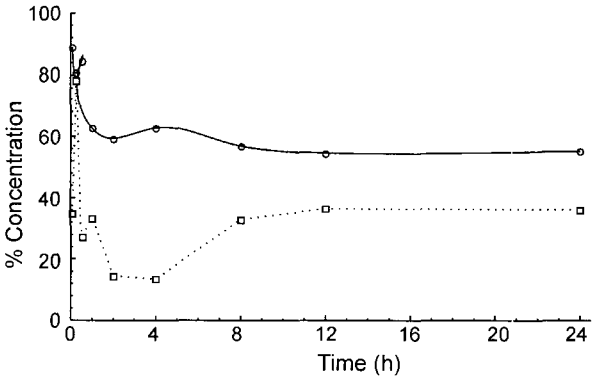



**Fig. 6.** 5-Fu concentration in mouse livers. Animals were given an intravenous injection of free 5-Fu ( □ ) or 5-FuS-SLN ( ○ ) (25 mg $kg^{-1}$ body weight). Samples were collected at the indicated time-points. Each point represents the ratio of 5-Fu concentration in liver to all organs and plamsa investigated.

injection study group was over two-fold of that of the 5-Fu injection study group (the former 67.3% and the latter 29.78%). The relative uptake rate ($r_e$=17.15) used to evaluate drug-targeting efficiency implied that 5-FuS-SLN had perfect liver targeting characteristics.

### Pharmacokinetics study

According to the chromatogram, the control plasma didn't affect sample separation and determination. The average recovery and accuracy of the determination method was 99.8±2.2%. The drug concentrations determined are presented in Table IV, which demonstrates that 5-FuS-SLN could change the concentration-time curve and the drug concentration in rabbits. Two groups both fitted the two-compartment model using the 3p87 program. The equations were $C=67.32e^{-4.271t}+1.470e^{-0.099t}$ and $C=21.08e^{-8.58t}+1.98e^{-0.540t}$. The parameters are shown in Table V. Pharmacokinetic study suggested that the drug concentration in rabbits of the 5-FuS-SLN study group was distinctly lower than that of the control group. It also implied that 5-FuS-SLN had the propensity to accumulate in the viscera of rabbits, which can lessen the drug toxicity. The possible explanation of the result was: after administration, 5-FuS-SLN was uptaken rapidly, especially into liver and spleen by the reticuloendothelial system (RES). SLN internalized in kupffer cells could release 5-Fu, and part of the released 5-Fu might diffuse to hepatic cells and play an anti-metabolite role.

**Table IV.** Concentration of 5-Fu in plasma after i.v. administration of 5-Fu injection and 5-FuS-SLN freeze-dried injection in rabbits (Mean±SD, n=5)

| Time (h) | 5-Fu injection (μg/mL) | 5-FuS-SLN (μg/mL) |
|---|---|---|
| 0.083 | 44.14±9.01 | 12.20±3.94 |
| 0.25 | 28.05±7.35 | 4.201±1.62 |
| 0.5 | 9.937±1.79 | 1.778±0.686 |
| 1.0 | 2.078±0.479 | 1.239±0.527 |
| 2.0 | 1.276±0.207 | 0.541±0.193 |
| 3.0 | 0.685±0.125 | 0.449±0.123 |
| 4.0 | 0.343±0.081 | 0.319±0.126 |
| 8.0 | n.d. | 0.106±0.007 |

n.d.=not detectable

**Table V.** Pharmacokinetic parameters of 5-Fu after i.v. administration of 5-Fu injection and 5-FuS-SLN freeze-dried injection in rabbits (Mean±SD)

| Pharmacokinetic Parameters | 5-FuS-SLN | 5-Fu |
|---|---|---|
| A (mg/L) | 21.08±0.619 | 67.32±7.070 |
| α (1/h) | 8.588±0.469 | 4.271±0.291 |
| B (mg/L) | 1.982±0.258 | 1.470±0.166 |
| β (1/h) | 0.5401±0.106 | 0.099±0.015 |
| $V_d$ (L/kg) | 0.0434±0.001 | 0.363±0.024 |
| $t_{1/2\alpha}$ (h) | 0.0807±0.011 | 0.162±0.009 |
| $t_{1/2\beta}$ (h) | 1.283±0.112 | 6.980±0.586 |
| AUC (mg·min/L) | 6.125±0.354 | 30.56±2.884 |
| CL (mL/min·kg) | 0.1633±0.018 | 0.818±0.056 |

A and B, intercepts of 5-Fu plasma concentration (at time zero) of compartment A and compartment B, respectively; α and β, the corresponding elimination rate constant. Abbreviations: $t_{1/2}$, half-life; AUC, area under the concentration curve; CL, total systemic clearance; $V_d$, volume of distribution. Mean pharmacokinetic parameters ±SD derived from animals administered with 5-FuS-SLN or 5-Fu (n=5) and were calculated by applying a two-compartment model.

## CONCLUSIONS

The potential usefulness of solid lipid nanoparticles as drug carriers has attracted increasing attention during recent years. The present study indicates that synthesis of the prodrug 5-FuS and preparation of 5-FuS-SLN could concentrate 5-Fu into liver tissue and control its release. Compared with 5-Fu injection, the study on the distribution of 5-FuS-SLN in mice showed that 5-FuS-SLN could increase 5-Fu concentration in mice liver two fold. Therefore the antitumor effects of 5-Fu might be prolonged and its adverse effects might be decreased. Further work needs to be done to understand the interaction of 5-FuS-SLN within a biological surrounding. However, the employment of the prodrug to enhance drug liposoluble properties and the preparation method presented here, seem to be an alternative strategy to the traditional colloidal delivery system.

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