Preparation and Evaluation of Solid-Self Emulsifying Drug Delivery System for Enhancing Bioavailability and Lymphatic Delivery of Paclitaxel

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ABSTRACT SUMMARY
We prepared and characterized the solid-self emulsifying drug delivery system (S-SEDDS) by spray drying method in order to improve the bioavailability (BA) and lymphatic delivery of paclitaxel. The mean droplet size, zeta potential, encapsulation efficiency, differential scanning calorimeter and X-ray diffractometry were measured. And in vitro and in vivo studies were conducted. The prepared S-SEDDS formulation showed significantly higher lymphatic targeting efficiencies than those of paclitaxel solution at the lymph node.

INTRODUCTION
Paclitaxel is active in metastatic breast cancer and is under evaluation for adjuvant and neoadjuvant treatment of early breast cancer. However, orally administered paclitaxel presents a major therapeutic problem because of low BA. It was reported that paclitaxel has a very low level of oral BA, at less than 10%. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant and/or co-solvents, and a drug that spontaneously form an oil-in-water nanoemulsion upon gentle agitation with water. When dispersed in the gastrointestinal (GI) tract, the motility of stomach provides necessary agitation for emulsification. SEDDS incorporated with a poorly water soluble drug demonstrate improved drug absorption since they maintain the drug in a solubilized state in the GI tract. However, since SEDDS have high surfactant concentrations, the large quantity of surfactant in self-emulsifying formulation irritates GI tract and volatile co-solvents migrate into the shell of gelatin capsules, resulting in the precipitation of the lipophilic drugs. To overcome these problems, S-SEDDS have been investigated as an alternative approach. S-SEDDS combine advantages of SEDDS with those of solid dosage forms. In this study, we prepared and characterized the S-SEDDS by spray drying method because of its simplicity. The objects of the present investigation were to develop S-SEDDS for increasing drug efficiency and decreasing side-effects by improving BA and targeting intestinal lymphatic system based on lipid formulation basis and to evaluate pharmacokinetic characteristics and targeting efficiency of prepared S-SEDDS.

EXPERIMENTAL METHODS
For the preparation of SEDDS, pseudo-ternary phase diagram studies were constructed to determine the high self-emulsifying composition, using the water titration method as described in previous studies. Pre-determined amount of oil-surfactant mixture was diluted with specific volume of deionized water in drop wise manner. The ratios of oil-surfactant mixture were varied from 1:9 to 9:1 at 10 percent increment. The nature of the resultant emulsions was decided by turbidity and viscosity with naked eye.

For preparing S-SEDDS, spray dryer was used as main instrument and Aerosil 200 and dextran were used for the solid carrier. In the process, 1 mL of liquid SEDDS was diluted with 100 mL of de-ionized water containing 500 mg of Aerosil 200 or 2000 mg of dextran under gentle string. The suspension was then spray-dried under controlled conditions; inlet temperature, 140-150°C; outlet temperature, 70-80°C; rotational speed of peristaltic pump, 3 rpm; atomizing air pressure, 0.15-0.25 mPa; and spray nozzle diameter, 0.5 mm.

For the evaluation of S-SEDDS, in vitro studies using the USP paddle method were performed at 37 ± 0.5°C at 100 rpm in pH 1.2 and 6.8 buffer. S-SEDDS were filled in hard gelatin capsule. 1 mL sample was withdrawn at predetermined time intervals of 10, 20, 30, 45 and 60 min and replaced with fresh buffer. The samples were centrifuged at 3000 rpm for 2 min, and the drug concentration was determined using HPLC method.

For the in vivo studies, the femoral artery of rats was cannulated with polyethylene tube under light ether anesthesia. The rats were divided into two groups: (1) paclitaxel solution diluted with 1:1 blend of Cremophor EL and ethanol, (2) paclitaxel loaded S-SEDDS. A single dose (20 mg/kg as paclitaxel) of each formulation was orally given to rats at the same time. At predetermined time intervals (0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hr), whole blood samples were withdrawn via femoral artery into Vacutainer tube with EDTA, then centrifuged (3000 rpm, 10 min) immediately. To evaluate the lymphatic delivery of paclitaxel, at 4 hr after administration, whole blood was taken from the abdominal aorta, then mesenteric and axillary lymph nodes were isolated and weighed. These lymph node
samples were suspended by homogenization for 1 min in a phosphate buffered saline (PBS, pH 7.4) so as to achieve final concentration of 25 mg/mL in the suspension and stored at -20°C. The concentrations of rat plasma or lymph node suspension samples were determined using HPLC method.

RESULTS AND DISCUSSION

Ternary phase diagrams of ethyl oleate, water, surfactants mixture (Tween80 + carbitol) with 90:10, 95:5 and 100:0 ratios shown in Figure 1. The self-emulsifying region was largest in ethyl oleate + Tween80:carbitol = 90:10 ratio.

In vitro studies, the release ratios of paclitaxel loaded S-SEDDS in pH 1.2 and pH 6.8 reached to 70 and 75 percent within 1 hr and 30 min, respectively. Dramatic increase in the rate of release of paclitaxel from S-SEDDS compared to paclitaxel powder due to the small droplet size, which permits a faster rate of drug release into aqueous phase and it could affect the bioavailability. And the release rate of paclitaxel in pH 6.8 buffer was higher and faster than that in pH 1.2 buffer.

In vivo studies, we found that the paclitaxel concentration increased significantly from 84.6 ± 4.1 ng/mL to 259.5 ± 7.5 ng/mL (Figure 2). This means that S-SEDDS have increased the BA of paclitaxel.

For lymphatic delivery (mesenteric and axillary) effect of S-SEDDS, the concentrations after administration of paclitaxel loaded S-SEDDS to rats were significantly increased than those of reference solution in both lymph nodes. The lymphatic targeting efficiencies of paclitaxel calculated as the ratio of the lymph node concentration to the plasma concentration are shown in Figure 3. Paclitaxel loaded S-SEDDS showed higher lymphatic targeting efficiencies than those of reference solution. In mesenteric lymph nodes, there was significant difference (P ≤ 0.05) between paclitaxel loaded S-SEDDS and reference solution.

CONCLUSION

Our studies confirmed that prepared S-SEDDS can be used as a possible alternative to conventional oral formulation of paclitaxel. Furthermore, it suggests that S-SEDDS can be explored as a potential drug carrier for other lipophilic drugs.

REFERENCES

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