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

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ABSTRACT SUMMARY

In order to improve the therapeutic efficacy of cyclosporine A (CyA) and decrease its side effects, we prepared and characterized the solid-self emulsifying drug delivery system (S-SEDDS) by spray drying method, and evaluated for enhancing bioavailability (BA) and lymphatic delivery by in vitro and vivo studies. The mean droplet size, zeta potential, encapsulation efficiency, differential scanning calorimeter and X-ray diffractometry were measured. The prepared S-SEDDS formulation showed significantly higher lymphatic targeting efficiencies than those of CyA solution at the lymph node.

INTRODUCTION

Cyclosporin A is used as an oral immunosuppressors for organ transplantation of liver, kidney, and bone marrow, and for the treatment of autoimmune disease and inflammation. However, the oral administration of CyA has various (from 3 to 87%) and low (average approximate 28%) BA. In order to improve BA, much attention has been focused on self-emulsifying drug delivery systems (SEDDS). 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. However, this formulation has some disadvantages including low drug compatibility, poor stability, drug leakage and precipitation, capsule aging, and high production costs. To overcome these problems, S-SEDDS have been investigated as an alternative approach. S-SEDDS combines 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 bioavailability and targeting intestinal lymphatic system based on lipid formulation basis.

EXPERIMENTAL METHODS

For the preparation of SEDDS, oil phase and surfactants screening was conducted. An excess amount of CyA was added to conical tube (Corning, NY, USA) containing 5 mL of each oil, surfactant, and co-surfactant. The mixtures were kept at 37 ± 1°C in water shaker for 3 days to reach equilibrium. After reaching equilibrium, each sample was centrifuged at 15,000 rpm for 10 min to remove the unsolved CyA, and the supernatant was collected. Each sample was injected in HPLC. And by changing the ratios of each compounds, droplet size and drug capacity were measured.

For preparing S-SEDDS, spray dryer was used as main instrument and Aerosil 200 was used for the solid carrier. In the process, 2 g of liquid SEDDS was diluted with 100 mL of de-ionized water containing Aerosil 200 under gentle stirring for 2 hr. The mixture was then sprayed through a nozzle onto the surface of fluidized cores. The conditions for this preparation are: inlet temperature, 150-155°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. The prepared S-SEDDS formulations were store at 25°C.

For in vitro release studies, CyA-loaded S-SEDDS and Cipol® capsule were tested using the paddle method at 37 ± 1°C at 100 rpm in pH 1.2 and pH 6.8 buffer. During study, 1 mL of sample was withdrawn at time intervals of 5, 10, 20, 40 and 60 min and replaced with fresh buffer. The concentration of CyA was determined using HPLC.

For in vivo studies, we divided into two groups (each six rats), CyA-loaded S-SEDDS and Cipol® group. A single dose (15 mg/kg) of each formulation was orally given to rats at the same time. After 0.5, 1, 2, 3, 5, 8, 12 and 24 hr the whole blood samples were withdrawn via femoral artery into Vacutainer® tube with EDTA, and stored at 4°C until assay by HPLC. Next, in order to evaluate the lymphatic delivery of CyA, whole blood samples at 3 hr were taken via abdominal aorta, then lymph nodes such as mesenteric and axillary lymph node were isolated and weighed. The main targeting efficiency of CyA to the lymphatic system was calculated as the ratio of CyA concentration in lymph node to the concentration in rat whole blood at 3 hr after oral administration of each formulation.
RESULTS AND DISCUSSION

S-SEDDS were prepared by spray drying method. The optimal solid carrier concentration was determined to 20% of Aerosil 200.

The droplet sizes and zeta potential of blank S-SEDDS in de-ionized water were 73.14 ± 2.77 nm and -34.43 ± 0.30 mV, respectively (n = 5). And the droplet sizes and zeta potential of CyA loaded S-SEDDS in de-ionized water were 79.37 ± 1.32 nm and -42.65 ± 2.85 mV, respectively.

In vitro dissolution profiles of CyA-loaded S-SEDDS in comparison to its commercial capsule, Cipol® capsule, in pH 1.2 hydrochloride and pH 6.8 phosphate buffer are shown at Figure 1.

![Figure 1](image1)

Figure 1. In vitro dissolution profiles of CyA from S-SEDDS and Cipol® capsule in (A) pH 1.2 hydrochloride and (B) pH 6.8 phosphate buffer. Each value represents the mean ± S.D (n = 12). * P ≤ 0.05.

Figure 2. Whole blood concentration-time curves of CyA after oral administration (15 mg/kg) of S-SEDDS (●) and Cipol® capsule solution content (○) to rats. Each value represents the mean ± S.D (n = 6). * P ≤ 0.05.

Figure 3. Lymphatic targeting efficiencies of CyA to mesenteric and axillary lymph nodes at 3 hr after oral administration (15 mg/kg) of Cipol® capsule solution content (■) and S-SEDDS (■) to rats. Vertical bars represent the mean ± S.D (n = 6). * P ≤ 0.05.

CONCLUSION

We confirmed that S-SEDDS preparation can improve bioavailability and lymphatic delivery of CyA. Furthermore, it suggests that S-SEDDS can be explored as a potential drug carrier for other lipophilic drugs.

REFERENCES


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