Preparation and Evaluation of Self-Microemulsifying Drug Delivery System (SMEDDS) containing Atorvastatin and Ezetimibe

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ABSTRACT SUMMARY

The aim of present study was to formulate self-microemulsifying drug delivery system (SMEDDS) fixed dose combination of atorvastatin calcium (ATV) and ezetimibe (EZT) for enhancing aqueous solubility of the drugs. Candidates of oil, surfactant and co-surfactant were screened to find out an optimal combination comprising SMEDDS. The formulation composed of ethyl oleate, tween 80 and PEG 600 was selected as a best formulation which formed stable microemulsion after addition of water through pseudo ternary phase diagrams. To evaluate SMEDDS formulations, size of microemulsion after dispersion and dissolution of active pharmaceutical ingredients (APIs) from SMEDDS were investigated. As a result, prepared SMEDDS showed extremely small droplet size. SMEDDS showed faster dissolution behavior compared with commercial products, Lipitor\textsuperscript{8} and Ezetrol\textsuperscript{9}. In conclusion, SMEDDS fixed-dose combination of ATV and EZT was formed stable microemulsion after and fast dissolution behavior, so it would be expected enhancing therapeutic effect of APIs.

INTRODUCTION

Hyperlipidemia is a physiological state of abnormally elevated levels of lipids and lipoproteins in the blood. The high lipid level not only results in lipid accumulation in artery lesions, but itself produces endothelial injury which is accompanied by platelet consumption and a hardening of the arteries.\textsuperscript{1}

ATV is a fully synthetic HMG-CoA reductase inhibitor that competitively blocks synthesis of cholesterol in liver. EZT inhibits cholesterol uptake by binding to a specific transport protein in the wall of the small intestine. Co-administration of ATV and EZT offers highly efficacious new treatment option for patients with hypercholesterolemia.\textsuperscript{2} However, both drugs have low solubility in water, so increasing their solubility is essential to increase of their therapeutic effects.

In the present study, SMEDDS was applied to increase solubility of the drugs. SMEDDS is isotropic mixtures of oil, surfactant, co-surfactant and API that form fine O/W emulsion when introduced into water phase with mild agitation.\textsuperscript{3} SMEDDS formulations would be beneficial to solubilize ATV and EZT.

EXPERIMENTAL METHODS

The solubility of ATV and EZT in various oils, surfactants and co-surfactants was determined. An excess amount of ATV and EZT was added to the excipients. After shaking at 40 °C for 72 h, the samples were centrifuged (5000 rpm, 10 min) and excess insoluble drug particles were discarded by filtration. The concentration of drugs was determined by a validated HPLC method after dilution.

SMEDDS was prepared by mixing of oil, surfactant and co-surfactant and then certain amount of ATV was added, followed by the addition of EZT. The mixture was mixed by a magnetic stirrer and completely dissolved in the system.

Pseudo-ternary phase diagrams of oil, mixture of surfactant/co-surfactant and water were constructed using water titration method to determine the optimized formulation of SMEDDS. The region of the microemulsion domain in the triangular diagrams was determined where formulation is visually transparent at ambient temperature. The ratios of surfactant to co-surfactant (S/CoS) were 5:1, 3:1, 1:1 and 1:3 (w/w). The percentage of microemulsion was calculated by using Image-Pro\textsuperscript{®} Express software.

Droplet size of SMEDDS formulations were analyzed using dynamic light-scattering techniques (Zetasizer Nano-S90, Malvern Instruments, Ltd.).

Morphology of SMEDDS formulation was recorded with field emission transmission electron microscopy (TEM, JEM-2100F, JEOL) operating at 25 °C, 200 kV.

The dissolution rate of drugs from SMEDDS and commercial products (Lipitor\textsuperscript{8} and Ezetrol\textsuperscript{9}) was evaluated according to FDA-recommended methods. The SMEDDS samples were filled into hard gelatin capsule for the testing. Samples were withdrawn at predetermined time intervals of 5, 10, 15, 30, and 60 minutes and analyzed by a validated HPLC method.

RESULTS AND DISCUSSION

Determination of optimized SMEDDS formulation is necessary to achieve maximum solubility of ATV and EZT concurrently. Capryol 90, ethyl oleate and castor oil showed the highest solubilization capacity among oils for ATV and EZT. Thus, they were selected for further studies. The excipients were chosen that Solutol HS 15, Labrasol and Tween 80 as surfactant and Capmul C8, Akoline MCM and PEG 600 as co-surfactant.
A series of SMEDDS were prepared, and their self-emulsifying properties were visually observed. Especially, ethyl oleate was well incorporated in Tween 80 and PEG 600, and it showed 64.5% of microemulsion region with the ratio of 5:1 for S/CoS (Fig. 1). After 1/10 dilution with water, the formulations containing 10 or 20% oil content stayed transparent as stable microemulsion during 24 hours. From the results, Ethyl oleate-Tween 80-PEG 600, S/CoS=5:1 formulation was selected for an optimum SMEDDS formulation and further evaluation studies.

Fig 2 (a) showed the mean droplet sizes of SMEDDS with various oil contents dispersed in three kinds of solvents (1:100). The size of droplets was below 40 nm at all oil contents. Also, SMEDDS formulation containing 20% of oil was stable in water, SGF and SIF at least for 12 hours, as shown in Fig 2(b), and it would be stable during administration and absorption in gastrointestinal tract. The droplet size according to dispersion medium was significantly different each other (ANOVA, p<0.05). However, the droplet size was below 50 nm in various medium, and it means stable microemulsion was formed.

The morphology of dispersed SMEDDS was evaluated by TEM and demonstrated in Fig 3. SMEDDS showed uniform and spherical emulsion structure with size of below 50 nm.

In vitro drug release profiles were examined to evaluate solubilizing effect of SMEDDS capsule and to compare with commercial products. The dissolution profile of SMEDDS capsule was faster than that of commercial products, as shown in Fig. 4. The f2 values (similarity factor) with Lipitor® and Ezetrol® are 48.3 and 32.0 indicating drug dissolution of SMEDDS capsule was different from that of commercial product. From the results described above, SMEDDS capsule was quickly dispersed in the medium into nano-sized emulsion and consequently showed faster dissolution rate. The large interfacial surface area derived from nano-sized droplets enable rapid release of drug molecules from SMEDDS formulations.

CONCLUSION
The SMEDDS fixed-dose combination of ATV and EZT was successfully developed. Small size less than 40 nm was obtained after dispersion and maintained during 12 hours in water, SGF and SIF. Also, it showed the faster dissolution profile of the drug compared with the commercial products. The results obtained from the study revealed that SMEDDS fixed-dose combination of two drugs was formulated with desired particle size range, physical stability and the dissolution characteristics. It could increase solubility of the drugs and furthermore it could improve pharmaceutical effect of the drugs.

REFERENCES

ACKNOWLEDGMENTS
This study was supported by a grant from the Korean Health Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea (A092018)