Improved Supersaturation and Oral Absorption of Sirolimus by Amorphous Solid Dispersions
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Purpose
The present study aimed to investigate the effect of Eudragit® E/HCl (E-SD) on the degradation of sirolimus in simulated gastric fluid (pH 1.2), as well as to develop a new oral formulation of sirolimus using the E-SD solid dispersion to enhance oral bioavailability.

Methods
The effect of E-SD, Hydroxypropylmethyl cellulose (HPMC), and D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) on the degradation of sirolimus in solution was investigated. In addition, the effect of E-SD and HPMC on the recrystallization of a supersaturated sirolimus was investigated. Sirolimus-loaded solid dispersions were fabricated via the spray drying process. In vitro and in vivo characterization of the solid dispersions was conducted to focus on the effect of the E-SD solid dispersion on supersaturation and the oral absorption of sirolimus.

Results
The degradation of sirolimus occurred rapidly and the percent remaining was below 2% at 30 min. HPMC had no influence on degradation, while E-SD demonstrated a significant dose-dependent inhibitory effect. The enhanced stability of sirolimus with increasing amounts of E-SD could be attributed to the formation of micelle-like structures. E-SD solid dispersions were fabricated via the spray drying method. For comparison, sirolimus-loaded HPMC and HPMC/TPGS solid dispersions were also prepared. All solid dispersions had irregular-shaped particles with similar mean particle size (6–8 μm). Physico-chemical analysis demonstrated that sirolimus is amorphous in all solid dispersions. A kinetic solubility test demonstrated that the sirolimus/E-SD/TPGS (1/8/1) solid dispersion had a maximum solubility of 196.7 μg/mL within 0.5 h that gradually decreased to 173.4 μg/mL after 12 h. According to the dissolution study, the most suitable formulation was the sirolimus/E-SD/TPGS (1/8/1) solid dispersion in simulated gastric fluid (pH 1.2), owing to enhanced stability and degree of supersaturation of E-SD and TPGS. The blood concentration of the sirolimus/E-SD/TPGS (1/8/1) solid dispersion with the rapid drug absorption rate was dramatically higher than that of the physical mixture at all timepoints. The AUC₀→₁₂h, Cₘₐₓ, and Tₘₐₓ were 459.5 ± 93.6 ng·h/mL, 97.4 ± 19.2 ng/mL, and 1.2 ± 0.3 h, respectively. The oral absorption of the E-SD/TPGS (8/1) solid dispersion was significantly higher than that of the physical mixture and HPMC/TPGS (8/1) solid dispersion, with approximately 7.2- and 1.4-fold increases in AUC₀→₁₂h, respectively. The bioavailability of the sirolimus/E-SD/TPGS (1/8/1) solid dispersion was markedly higher than that of the physical mixture and sirolimus/HPMC/TPGS (1/8/1) solid dispersion, due to higher supersaturation and supersaturated concentration over an increased period of time, as well as enhanced stability in simulated gastric fluid (pH 1.2).

Conclusion
Therefore, these results demonstrated that dissolution and oral absorption of sirolimus can be enhanced by formulating it in the form of amorphous E-SD/TPGS solid dispersion nanoparticles manufactured using the spray-drying process.