A Mixed Micelle Formulation Strategy for Enhancing Oral Bioavailability of Berberine by Modulating P-glycoprotein
M. Kwon¹, Y. A. Choi², M-K. Choi², I-S. Song¹
¹Kyungpook National University, ²Dan-Kook University

Purpose
Berberine has long been used for treatment of bacteria-associated diarrhea and gastrointestinal infections in China. It shows wide range of pharmacological effects including hypolipidemic and hypoglycemic effects. However, low oral bioavailability (0.68 % in rats) is one of the major obstacles for market approval of berberine. Extensive intestinal first-pass effect was attributed to the low plasma level and, therefore, modulation of P-gp mediated efflux of berberine was regarded as a strategy for overcoming limited gastrointestinal absorption. The purpose of this study was to develop berberine formulation with enhanced oral bioavailability by using pharmaceutical excipients that have P-gp inhibitory effect.

Methods
To optimize the berberine formulation, studies on berberine solubility, cell viability for cytotoxic effect of excipients, and P-gp inhibitory effect were carried out in the presence of various compositions of pharmaceutical excipients including Pluronic P85 and tween 80. For the final formulation of berberine, in vitro intestinal permeability test using Caco-2 cells and in vivo pharmacokinetic studies in male SD rats were performed. Bidirectional transport rates of berberine and berberine formulation were measured in Caco-2 cell monolayers. Apparent permeability and efflux ratios of berberine were compared with those of berberine formulation. The rats were administered berberine itself at a single oral dose of 200 mg/kg and berberine formulation at a single oral dose of 50 mg/kg. Plasma and bile samples were collected for 12 h after the oral administration of berberine and berberine formulation. Berberine concentrations in the biological samples were analyzed by using liquid chromatography coupled with tandem mass spectrometry.

Results
Pluronic P85 and tween 80 were used as P-gp inhibitors and pharmaceutical excipients for mixed micelle formulation. The optimal micelle formulation of 1: 5: 0.5% (berberine: pluronic P85: tween 80, w/w/%) was selected based on P-gp inhibitory effect, berberine solubility enhancement, and least cytotoxicity. This optimized berberine mixed micelle formulation increased intestinal permeability of berberine and reduced efflux ratio of berberine in Caco-2 cells. Pharmacokinetic parameters were calculated by using non-compartmental analysis. Dose normalized area under the plasma concentration versus time profile of berberine in the treatment group of oral administration of berberine mixed micelle formulation was slightly increased compared with that in berberine control group. However excreted amounts of berberine and its metabolites via biliary route were profoundly increased in berberine mixed micelle formulation group compared with those in berberine control group. It suggests that increased intestinal permeability and absorption of berberine can be achieved through the berberine mixed micelle formulation with P-gp inhibitory effect. However, once berberine was exposed in the systemic circulation, berberine was extensively eliminated through the metabolism and biliary excretion. To retarded the extensive metabolism of berberine, berberine mixed micelle formulation was modified by addition of 0.03% sodium lauryl sulfate because it showed inhibitory effect of phase I metabolism (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A) and Phase II metabolism (UGT1A1, UGT1A4, UGT1A9, and UGT2B7).

Conclusion
Mixed micelle formulation of berberine ameliorating P-gp mediated efflux of berberine and phase I and Phase II enzyme mediated berberine metabolism was developed by using Pluronic P 85, tween 80, and sodium lauryl sulfate. Although the optimized formulation of berberine need to be further developed, our strategy for developing biopharmaceutical mechanism (i.e., P-gp mediated efflux and metabolism) based formulation would give a reasonable result for increased oral bioavailability and maintenance of therapeutic plasma concentrations of drug.