Effect of Particle Size on the Oral Absorption of Poorly Water-Soluble Drugs: In Vitro Assessment Using the Dissolution/Permeation System

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Purpose
In order to streamline the development of oral formulations which can improve the absorption of poorly water-soluble drugs, an in vitro method predictive for in vivo performance of various formulations is required at the early stage of the pre-clinical study. Among various formulation technologies, micronization is one of the most popular technologies applicable to various drugs. However, since the micronization primarily increases the dissolution-rate of drugs, but not their solubility, the potency of this technology largely depends on the physico-chemical properties of the drug as well as its clinical dose. The dissolution/permeation (D/P) system has been reported as a useful in vitro tool for prediction of oral absorption of drugs in humans by simultaneously analyzing the drug dissolution and the permeation process (1). In this study, the suspensions of fenofibrate, nifedipine or lovastatin with various particle sizes were prepared and their oral absorption was evaluated by the D/P system in vitro. Furthermore, rat oral absorption studies were performed to validate the in vitro-in vivo correlation (IVIVC) in the effect of the micronized formulation.

Methods
Fenofibrate, nifedipine and lovastatin were used as model drugs of poorly water-soluble drugs classified to BCS class 2. Aqueous suspensions of these drugs having four different particle sizes were prepared by using a vortex mixer (Suspension A), a Teflon/glass homogenizer (Suspension B), a mortar (Suspension C), and a rotation/revolution mixer (Suspension D). In the D/P system, the MDCKII cell monolayer was mounted in side-by-side chambers. Eight milliliters of modified fasted-state simulated intestinal fluid (FaSSIFmod, pH 6.5) and 5.5 mL of buffered solution (pH 7.4) containing 4.5% BSA were added to apical and basal sides, respectively. After applying 100 µL of the drug suspension to the apical side, the basal solution and the apical suspension were sampled over 2 h. Concentration of drugs in the basal and filtrated apical solution was analyzed using LC-MS/MS. In the in vivo study, the drug suspension was orally administered to Sprague-Dawley rats and the time-profile of drug plasma concentrations was determined to calculate the AUC after oral administration.

Results
For fenofibrate, the mean particle size in the Suspension A, B, C and D was 61, 20, 9, and 5 µm, respectively. Dissolution rate of fenofibrate in apical FaSSIF fluid increased as the mean particle size reduced and the immediate dissolution was observed in the Suspension D. Other suspensions showed slow dissolution and, in the apical side, the concentration of dissolved fenofibrate after 2 h in the Suspension A, B and C did not reach to that of Suspension D. Permeated amount (% of dose/2 h) of fenofibrate into the basal side increased with an increase in the dissolution rate. Another two drugs, nifedipine and lovastatin, showed similar results in vitro. The plasma AUCs of the three drugs after oral administration of each suspension to rats well correlated with the permeated amount in the D/P system (Fig. 1), indicating the good IVIVC in the effect of particle size on the oral absorption of BCS class 2 drugs.

Conclusion
These results indicated the advantage of using the D/P system for evaluating the effectiveness of micronized formulation as the in vivo predictive in vitro test.

![Figure 1. Relation between the permeated amount of drugs in D/P system and their plasma AUC in rats after oral administration](image-url)