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Evaluation of dose dependent oral drug absorption by µFlux

Shiori Ishida[1], Samuel Lee[2], Karl Box[2] , Balint Sinko[2], Kiyohiko Sugano[1]

[1]College of Pharmaceutical Sciences, Ritsumeikan University, Japan
[2]Pion UK Inc, Forest Row, United Kingdom

Introduction

The assessment of oral drug absorption is important in drug development. In this study, we evaluated the dose dependency of oral absorption by µFlux. µFlux can simultaneously measure the dissolution and permeation processes of oral drug absorption.

Method

Celecoxib (CEL) crystal formulation (50 to 900 mg in humans, 5 to 90 mg/vessel) and amenamevir (AME) solid dispersion formulation (100 to 600 mg in humans, 10 to 60 mg/vessel) were selected as model formulations. Each formulation was ground and added to the donor compartment. 15 mL of pH 6.5 FaSSIF was added into the donor compartment, and 15 mL of accepter sink buffer was added into the acceptor compartment (37 °C, 200 rpm). The membrane consisted of GIT-0-Liquid-Solution (1.54 cm^2). For amenamevir, the precipitates in the donor compartment were collected after 4 h and observed by polarized light microscopy.

Results

When the dose amount of CEL was increased by 8-fold, the flux value increased by approximately 2-fold, and AUC in clinical trials increased by approximately 6-fold. The drug concentrations dissolved in the donor compartment did not change at all doses. When the dose amount of AME was increased by 6-fold, the flux value in the initial phase (10 to 30 min) inceased by 1.3-fold, and AUC in the clinical trial increased by approximately 3-fold. However, the flux value decreased to the same value at all doses after 30 minutes. Crystal precipitant was observed in the donor compartment after 4 hours.

Discussion

In the case of CEL, the increase in the flux value was attributed to an increase in the effective membrane permeability due to drug particles drifting into the unstirred water layer. Because of the villi structure, the particle drifting effect would become more significant in vivo than in µFlux. For clinical Fa prediction, the theoretical framework for oral drug absorption (GUT framework) can be used to consider the effect of villi structure on the flux value.

In the case of AME, due to the insufficiency of permeation clearance, the dissolved drug concentration in µFlux would have been higher than that in humans, resulting in faster crystalline precipitation in µFlux and underestimating the increase in AUC. The adjustment of the dose/volume ratio may be required to reflect the effect of permeation clearance on the supersaturation–precipitation profile in humans.