Title	**Quantification of 2-hydroxypropyl-β-cyclodextrin in human intestinal fluids helps to understand the intraluminal drug behavior following the oral intake of Sporanox®**
Keywords	Itraconazole, hydroxypropyl-β-cyclodextrin, Sporanox®, human intestinal fluids, LC/MS-MS
Authors	Philippe BERBEN[1], Jef STAPPAERTS[1], Matthias VINK[2], Elena DOMINGUEZ-VEGA[2], Govert SOMSEN[2], Joachim BROUWERS[1], Patrick AUGUSTIJNS[1] *[1]Drug Delivery and Disposition, KU Leuven, Gasthuisberg O&N II, Herestraat 49 - box 921, 3000 Leuven, Belgium* *[2]Division of BioAnalytical Chemistry, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands*
Abstract	In a previously performed small-scale clinical study, healthy volunteers were asked to ingest an oral solution of itraconazole (Sporanox®) containing 40% 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) (i) with or (ii) without a standardized volume of water (240 ml) after which gastrointestinal and blood samples were collected[1]. Although omitting water during the administration of Sporanox® resulted in noticeable higher duodenal concentrations of itraconazole, systemic exposure was almost unaffected. It is assumed that this discrepancy can be explained by differences in the extent of entrapment of itraconazole in the duodenum caused by differential complexation depending on the concentration of cyclodextrins[2]. To further substantiate this hypothesis, the quantification of HP-β-CD concentrations in the aspirated intestinal fluids was performed by LC-MS/MS. When comparing the intestinal concentrations of itraconazole and HP-β-CD for one single healthy volunteer (HV02) in both test conditions, an excellent correlation was observed (Spearman's rank coefficient of 0.96). Moreover, the data suggest that, similar to aqueous buffer media, also in human intestinal fluids a non-linear relationship exists between itraconazole solubility and HP-β-CD concentration (A_p-type profile; Spearman's rank coefficient of 0.78), indicating that higher order complexes are formed at higher concentrations of HP-β-CD. This difference in extent of entrapment in the inclusion complexes helps to understand the observed impact of water intake on precipitation and permeation behavior of itraconazole in man. Without water intake, higher HP-β-CD concentrations resulted in less precipitation and increased duodenal concentrations of itraconazole. On the other hand, the stronger interaction at higher HP-β-CD concentrations reduced the free fraction of the drug explaining that increased intraluminal concentrations of itraconazole were not translated into an enhanced uptake. In conclusion, quantifying the concentrations of the solubilizing agent HP-β-CD in human intestinal fluids appeared to be of crucial importance to interpret the intraluminal behavior of an orally administered cyclodextrin-based solution.
References	1. *P. Berben, R. Mols, J. Brouwers, J. Tack, P. Augustijns, Gastrointestinal behavior of itraconazole in humans - Part 2: The effect of intraluminal dilution on the performance of a cyclodextrin-based solution, Int. J. Pharm. 526 (2017) 235–243.* 2. *M.E. Brewster, R. Vandecruys, J. Peeters, P. Neeskens, G. Verreck, T. Loftsson, Comparative interaction of 2-hydroxypropyl-beta-cyclodextrin and sulfobutylether-beta-cyclodextrin with itraconazole: phase-solubility behavior and stabilization of supersaturated drug solutions, Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci. 34 (2008) 94–103.*