Original Study of the Bioavailability Enhancement of Itraconazole-Based Solid Dispersions Produced by Hot Melt Extrusion in the Framework of the Three Rs Rule

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Purpose
During this project, amorphous solid dispersion (ASD) formulations made of itraconazole (ITZ) were produced using Hot Melt Extrusion (HME). Since ITZ possesses a water solubility of less than 1ng/mL, the aim of this work was to enhance the aqueous solubility of ITZ, and therefore improve its bioavailability. Soluplus® was chosen as the main excipient after a preformulation study. The three formulations consisted of a simple Soluplus®/ITZ ASD, an optimized Soluplus®/ITZ/ AcDiSol® (superdisintegrant) ASD obtained after performing a design of experiments and a formulation containing Soluplus®/ITZ and an equimolar amount of hydroxypropyl-β-cyclodextrin (substitution degree=0.63; ITZ:HβCD0.63 1:1 molar ratio). The in vitro enhancement of solubility was previously proven using a biphasic dissolution test.

During this study, the bioavailability of these three formulations was evaluated by in vivo administration to rats and compared to the marketed product Sporanox®. Moreover, the bioanalytical method was optimized so that only 10μL of blood was withdrawn from the rats using specific volumetric absorptive microsampling (VAMS) devices for each time point. This allowed us to keep the same rats during the whole study which is more ethical and in accordance with the three Rs rule (reduction, refinement and replacement). Moreover, this technique enabled us to suppress inter-individual variability.

Methods
The three ASDs were produced on an 18mm twin screw extruder (Scamex®). A common screw configuration with two kneading zones was used. Soluplus®/ITZ (75:25wt%) and Soluplus®/ITZ/ AcDiSol® (72.5:25:2.5wt%) were both produced at 155 °C and 100 rpm while Soluplus®/ITZ/HβCD0.63 (25:25:50wt%) was extruded at 190 °C and 150 rpm. The three ASD and Sporanox® were tested on 9 Wistar rats at a dose of 10mg/kg. Blood samples (10μL) were retrieved from the tail of the rats using Mitra® (Neoteryx®) devices. The VAMS were allowed to dry for 2h then ITZ and hydroxyl-ITZ were extracted by dipping the VAMS into a mixture of ACN/MeOH (60/40 v/v) during 5min. They were then further shaken during 5min and vacuum-filtered through a lipid removal plate (OTRO®). The samples were analyzed using a validated LC/MS method (internal standard 9-deuterated ITZ).

Results
In vitro dissolution results (Fig. 1) showed that the ASD produced by HME were better than Sporanox® with the following ranking: Soluplus®/ITZ/CD > Soluplus®/ITZ/AcDiSol® > Soluplus®/ITZ > Sporanox®. Regarding ITZ (Fig. 2) and hydroxyl-ITZ blood concentrations, the Cmax and AUC ranking were the following: Soluplus®/ITZ/ AcDiSol®> Soluplus®/ITZ/CD > Soluplus®/ITZ > Sporanox®. This means that the solubility enhancement observed in vitro was reflected in vivo. This can be explained by the fact that the superdisintegrant and CD enabled a fastest release of ITZ and therefore a fast absorption. However, the inversion in the ranking might be due to the interaction of CD with compounds present in biological fluids rather than with ITZ.

Conclusion
A pharmacokinetic study of ITZ in rats was conducted in the framework of the three Rs rule and Soluplus®/ITZ/ AcDiSol® was the best formulation in vivo which increased the bioavailability of ITZ by a factor 5 in comparison with Sporanox®.