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Differentiating Itraconazole Formulations Based on the Flux through Artificial Lipophilic Membrane

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PURPOSE

It was demonstrated[1,2] that flux measurements provide more in-depth understanding of supersaturated systems than solute concentration measurements alone. This study used miniaturized dissolution – permeation apparatus (µFLUX) to compare flux of itraconazole (Figure 1) from several formulations for which *in-vivo* rat PK data were available[3]. The goal of the study was to evaluate the formulation benchmarking ability of the instrumental setup.

METHOD

Nanoparticles of itraconazole (ITZ, 207 nm mean particle size) were prepared as 10 wt% suspensions in DI water with small amounts (< 3 wt%) of stabilizing excipients. Untreated (x_{50} = 17.8 µm) and micronized (x_{50} = 1.7 µm) powders of ITZ were suspended in the same media before the assay. Sporanox® solid dispersion commercial formulation and ITZ-Soluplus® solid dispersion extrudates[3] were assayed as milled and sieved powders. All formulations were introduced to the donor compartment of µFLUX apparatus (Pion Inc., Figure 2) containing 20 mL of FeSSIF at 0.4 mg/ml of ITZ. Donor and acceptor compartments were divided by a lipophilic membrane (Double-Sink™ PAMPA type) and flux was monitored. All measurements performed using the µDISS Profiler™ (Pion Inc.), and were done in triplicate at 37 ºC using a stirring speed of 150 rpm. Further solid state characterization (XRPD and DSC) were performed on ITZ solid dispersion formulations to better understand changes in flux observed over time. Therefore experiments were repeated using larger sample volumes. Suspended solids were isolated after 2 centrifugation-decantation cycles with washing in between, followed by freeze-drying.

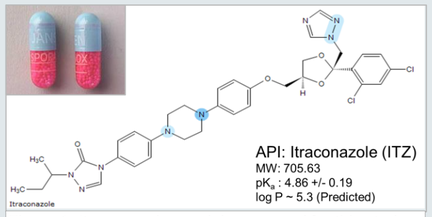


Figure 1. Itraconazole: model compound for this study.

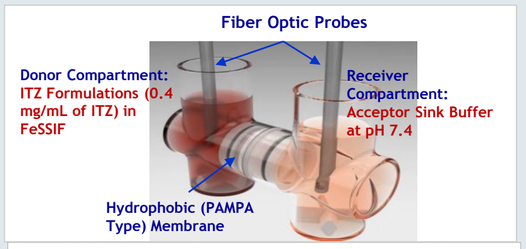


Figure 2. Schematic of µFLUX setup with some details of the assay setup.

RESULTS

COMPARATIVE FLUX ASSAYS

Concentration of ITZ in the receiver chambers was monitored with a dedicated blank pair (no ITZ) assessing integrity of the membrane and allowing additional correction for the background signal. Flux from both unformulated (0.006±0.002 µg $min^{-1}cm^{-2}$) and micronized (0.007±0.001 µg $min^{-1}cm^{-2}$) ITZ did not change over the duration of the experiment (Figure 3, 4). Initial flux (60 – 200 min) from nanosuspension formulation was 0.027±0.004 µg $min^{-1}cm^{-2}$ and showed a mild decreasing trend after about 3 hours to 0.019±0.002 µg $min^{-1}cm^{-2}$ (200 – 300 min).

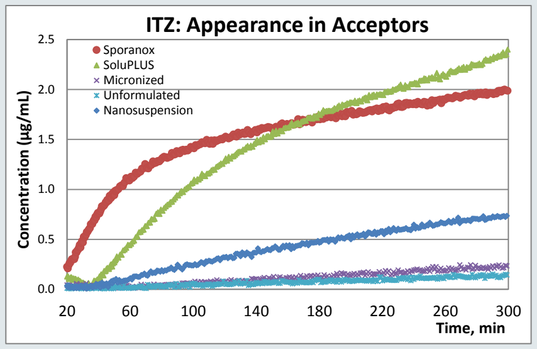
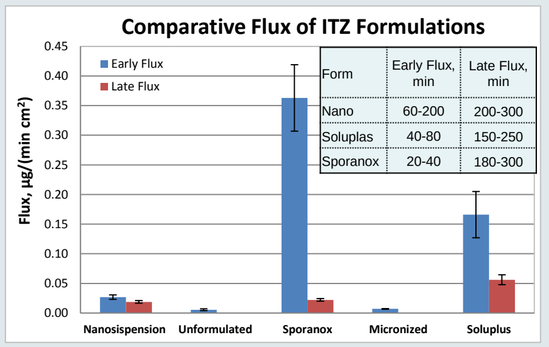


Figure 3. Example of concentration-time profiles of ITZ in the receiver chambers of µFLUX system from different formulations of ITZ



Form	Early Flux, min	Late Flux, min
Nano	60-200	200-300
Soluplas	40-80	150-250
Sporanox	20-40	180-300

Figure 4. Flux values at the beginning (blue) and at the end (brown) of the experiment. Error bar indicates SD from triplicate measurements and insert table shows time intervals used for flux calculations.

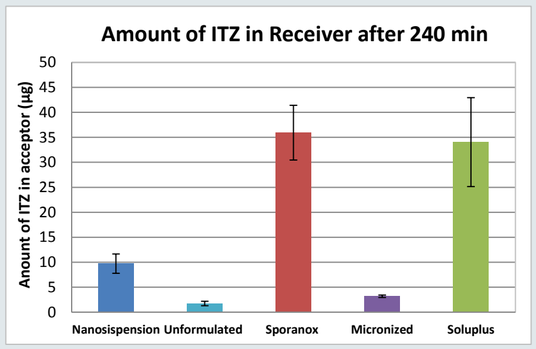


Figure 5. Total amount of ITZ in receiver compartments after 240 min of permeation experiment (average from triplicates with error bar indicating ±SD).

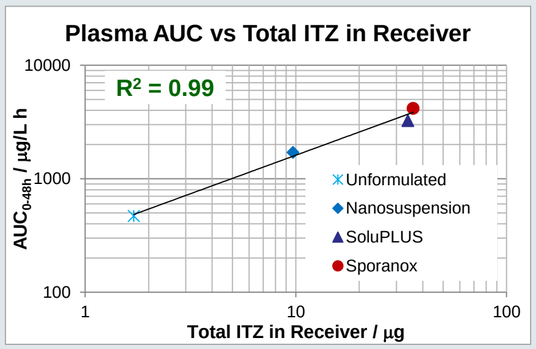


Figure 6. Log-log plot of AUC for ITZ from animal data[3] versus total amount of ITZ in receiver from µFLUX after 240 min. Color coding corresponds to Figure 5.

The Sporanox® formulation showed the highest initial flux of 0.363±0.056 µg $min^{-1}cm^{-2}$ but it was reduced to the flux similar to one of nanosuspension formulation after ~ 2.5 hours of the experiment. Although initial flux of the Soluplus® ITZ formulation (0.166±0.039 µg $min^{-1}cm^{-2}$) was lower than one for Sporanox®, it was not reduced so drastically after initial period and was 0.056±0.008 µg $min^{-1}cm^{-2}$ after ~ 2.5 hours (Figures 3-4). As a further example of the rank-ordering potential of the technique, the total amounts of ITZ in the receiver compartment after 240 min were evaluated (Figure 5). For Sporanox® and Soluplus® formulations, comparable results were obtained: 36.0±5.5 µg and 34.0±8.9 µg respectively. Amounts of permeated ITZ from other formulations were 9.7±1.9 µg (nanosuspension), 3.2±0.3 µg (micronized powder) and 1.7±1.5 µg (untreated powder). Thus, total amount of material in the receiver chamber at 240 minutes showed the same rank order as observed in the *in-vivo* PK data[3] (Figure 6).

RESULTS

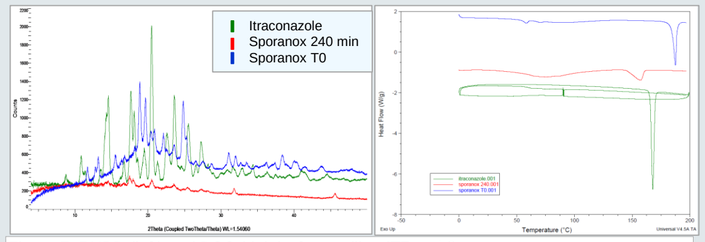


Figure 7. RXPD (left) and DSC (right) of crystalline ITZ and Sporanox.

Sporanox® solid dispersion, XRPD:
- Crystallinity in blue is not from ITZ (green)
- ITZ crystallinity observed in suspended sample (red; peaks around 32 and 45 °2theta are artifacts)

Sporanox® solid dispersion, DSC:
- Melting original powder (blue) is from sucrose, not ITZ (green)
- Glass transition in original powder
- Water evaporation + ITZ melting observed in suspended sample (red)

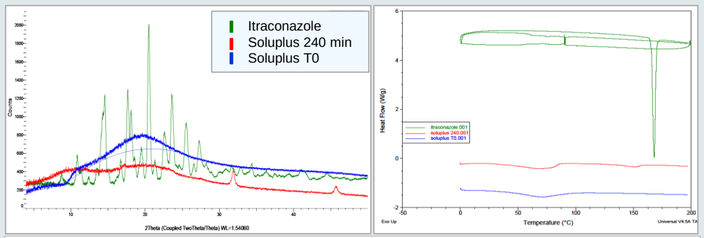


Figure 8. RXPD (left) and DSC (right) of crystalline ITZ and Soluplus ASD.

Soluplus® solid dispersion, XRPD:
- No observation of crystallinity (peaks around 32 and 45 °2theta are artifacts)

Soluplus® solid dispersion, DSC:
- No melting in original powder (blue)
- Water evaporation + ITZ melting observed in suspended sample (red; note: melting was much clearer for 30 mins sample)

CONCLUSION

It was demonstrated that *in vitro* flux measurements using lipophilic artificial membranes could correctly reproduce rank order of rat PK results for different ITZ formulations. The drop in flux over time for solid dispersions could be backed by experimental indications of precipitation.

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