Using flux experiments through artificial lipophilic membranes for predicting food effect for BCS Class 2 Compounds

OksanaTsinman[1], Konstantin Tsinman[1*], Ram Lingamaneni[1]

***presenting author; ktsinman@pion-inc.com; [1]Pion Inc., 10 Cook Str., Billerica, Ma 01821, USA;**

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PURPOSE

The food effect on absorption can be attributed to the different mechanisms and it is often difficult to predict while pharmacokinetic (PK) studies are expensive and may have big variability. Recent studies[1] demonstrated that flux measurements provide better insight into complex relationship between thermodynamic activity and equilibrium solubility of the low soluble compounds in the presence of excipients (e.g. components of the simulated intestinal fluids).

This work aimed to introduce an *in vitro* method for qualitatively estimating food effect in early stages of pre-formulation and formulation based on the differences in the flux through artificial lipophilic membranes of two chamber dissolution-permeability system.

METHOD

BCS class 2 drugs (Figure 1) Danazol (DNZ, MW 337.5, non-ionizable in pH 2.0 – 9.0 range, logP 4.5); Griseofulvin (GSF, MW 352.8, no ionizable groups, logP 2.2); Phenytoin (PHT, MW 252.3, pK_a 8.2, logP 2.2) and 2 formulations of Itraconazole (ITZ, MW 705.64, pK_a 3.7, logP 5.6) Sporanox solid dispersion commercial formulation (milled & Sieved) and ITZ-Soluplus solid dispersion extrudates were used as a model compounds for this study. All pure API and formulations of ITZ were delivered in the donor compartment of µFLUX apparatus (Figure 2, Pion Inc.) containing 20 mL of FaSSIF or FeSSIF media at the loads DNZ (0.4 mg/mL); GSF (0.6 mg/mL); PHT (1.4 mg/mL) and ITZ (0.4 mg/mL) respectively. The acceptor compartment contained 20 mL of Acceptor Sink Buffer (ASB pH 7.4, Pion Inc.). Donor and acceptor compartments were separated by a lipophilic membrane (Double-Sink™ PAMPA type) and concentration in both chambers was monitored using *in situ* fiber optic technique (µDISS Profiler™, Pion Inc.). The ratio of the flux from FeSSIF media to the one from FaSSIF was used as an indicator of positive, negative or neutral food effect.

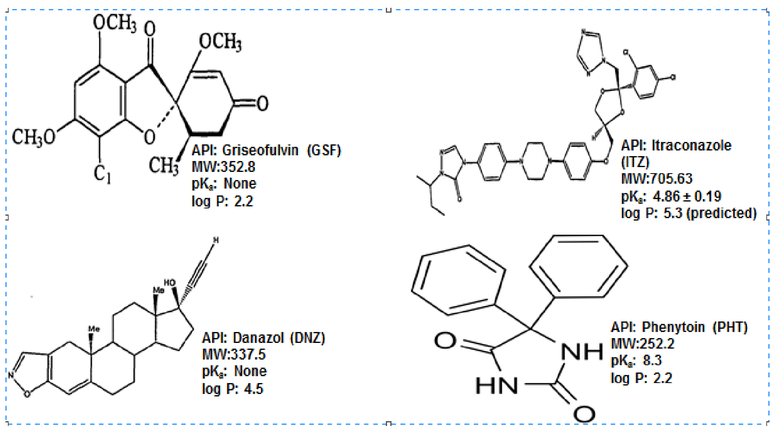

Figure 1. Samples used for the study.

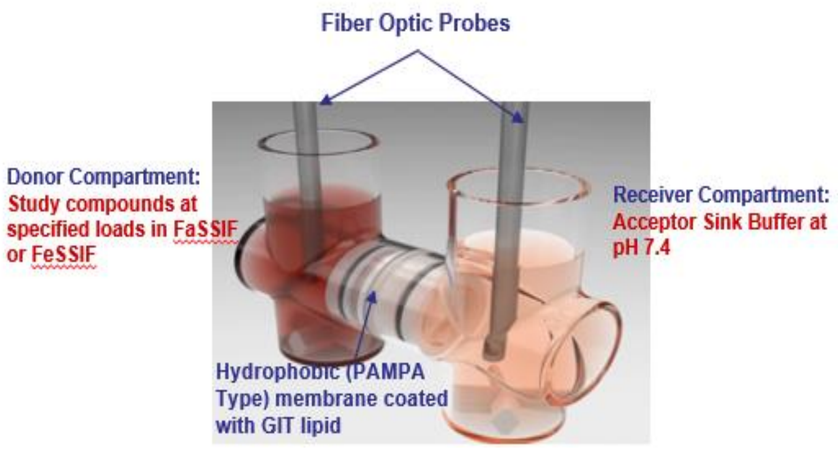

Figure 2. Schematic of µFLUX setup during the assays.

RESULTS

COMPARATIVE FLUX ASSAYS SUMMARY

The model compounds used for the study demonstrated that the flux assays are robust tool in estimating food effect on drug absorption in preformulation and formulation settings, even in cases like PHT and ITZ where dissolution data may not be reliable due to huge amount of turbidity from the undissolved API. The comparative flux summary of the study compounds and amount of material appeared in the acceptor at 4 hour time point are shown in the Figures 3 and 4 below.

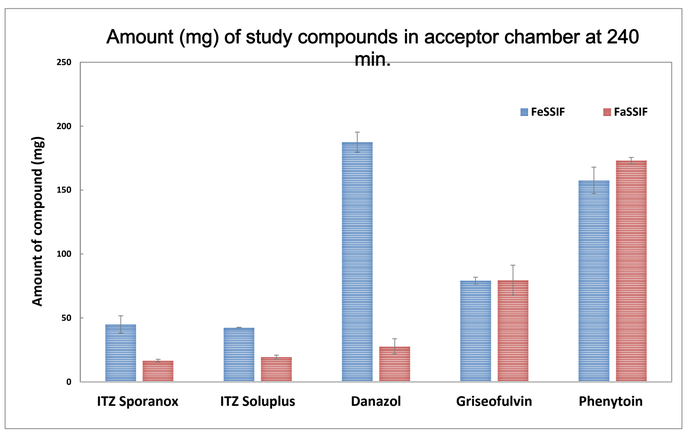

Figure 3. Total amount of compounds in the receiver compartments after 240 min of the flux experiment (average from 2 replicates with error bar indicating ±SD).

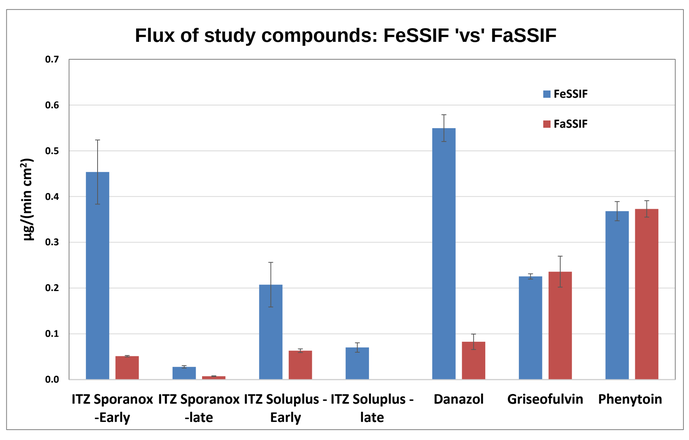

Figure 4. Flux values for the study compounds with FeSSIF (blue) and FaSSIF (brown) media in the donor. Error bars indicates SD from the n = 2 measurements.

Danazol: Maximum concentration of DNZ in the donor compartment containing FeSSIF was 30 µg/mL (7.5% dissolved) while in FaSSIF its concentration reached only 8 µg/mL (2% dissolved). Correspondingly the flux of DNZ from FeSSIF was 0.55±0.03 µg $min^{-1}cm^{-2}$ comparing to 0.08±0.02 µg $min^{-1}cm^{-2}$ from FaSSIF. Strong positive food effect (~3 fold) for DNZ was also reported for *in vivo* studies[2].

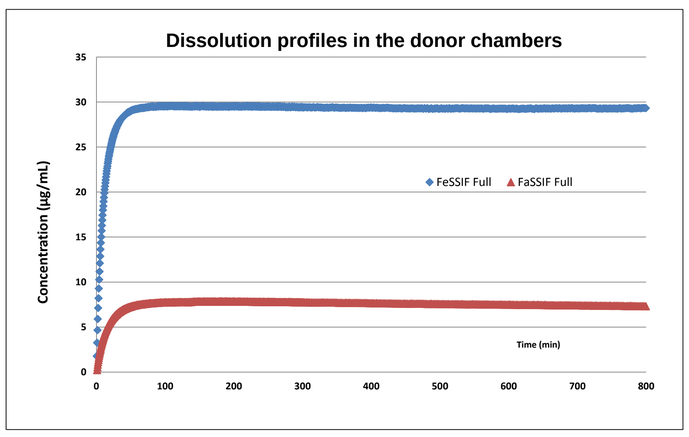

Figure 5. Dissolution profiles of DNZ in FeSSIF and FaSSIF at 0.4 mg/mL load in donors during µFLUX experiment (average of 2 replicates).

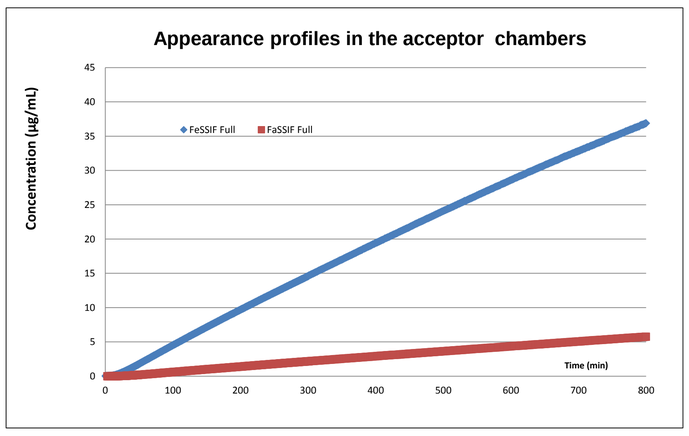

Figure 6. concentration-time profiles of DNZ in the receiver chambers of µFLUX system (average of 2 replicates)

RESULTS

Phenytoin: Dissolution profiles of PHT in donors could not be characterized at the load of 0.6 mg/mL used during the flux experiments. However the amount of PHT in permeated to the receivers at 240 min from FeSSIF (~157 µg) was very close to the amount from the FaSSIF (~173 µg). No marked difference was observed in flux among the two media (Figure 4) supported by mild food effect (~1.9 times) reported in literature[2].

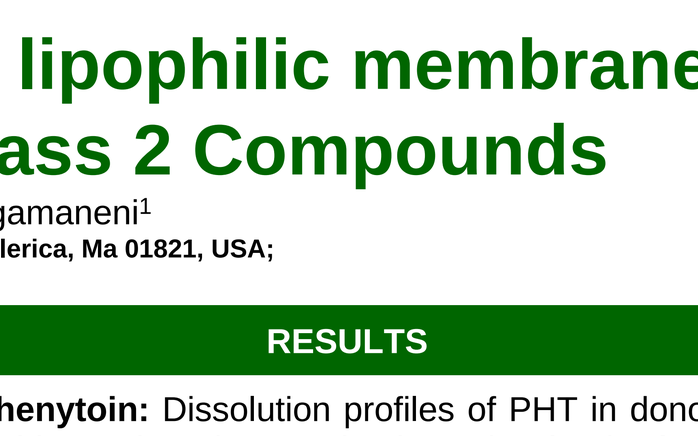

Figure 7. Concentration-time profiles of PHT in the receiver chamber of µFlux system (average from 3 replicates).

Itraconazole Formulations (Sporanox and ITZ-Soluplus Extrudate):

ITZ-Sporanox and ITZ-Soluplus extrudates showed similar behavior with higher but changing flux in FeSSIF and lower, but almost constant flux in FaSSIF (Figure 8). The difference in flux between the formulations and media was confirmed by the amount of ITR appeared in receiver chambers at 240 min shown in the Figure 3. Both formulations of ITR exhibited ~2.5 times increase in both flux and total amount absorbed, which is in agreement with the reported (~3 fold) food effect for ITR in the literature[3].

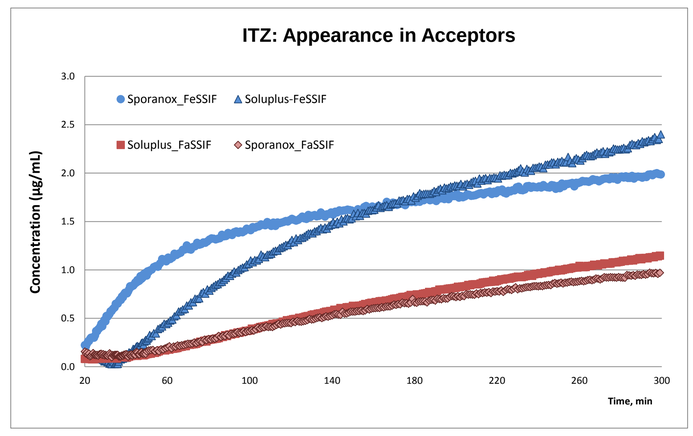

Figure 8. An example of concentration-time profiles of ITR formulations in the receiver chamber of µFlux system.

CONCLUSION

It was demonstrated that *in vitro* flux measurements using lipophilic artificial membranes could be a useful tool in studying and understanding effect of FaSSIF/FeSSIF components (i.e. lecithin and bile salts) on potential change in the drug absorption. The difference in the flux between FeSSIF and FaSSIF could become an early risk indicator when predicting food effect on the absorption of BCS class 2 drugs. More studies are needed to establish rank ordering rules for the food effect risks and to include drug product formulations in the considerations.

REFERENCES

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