USE OF IN-VITRO DISSOLUTION AND FLUX FOR SELECTION OF BIOAVAILABILITY ENABLING FORMULATIONS

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Figure 1: Dissolution/Flux vs Micelle Bound Fraction

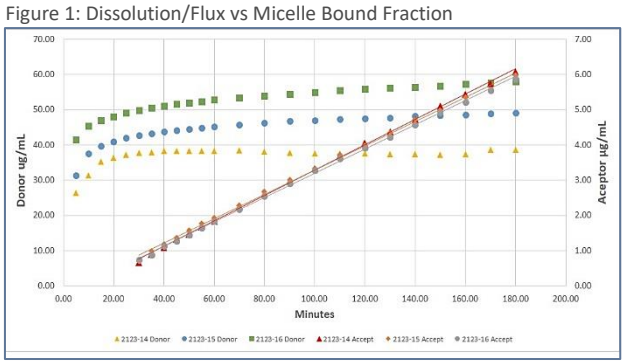

Figure 2: Flux vs Free/Dissolved Donor Concentration

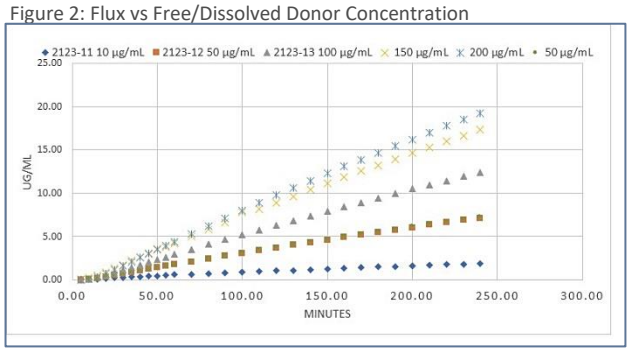

Figure 3: Flux Regression Model Comparison

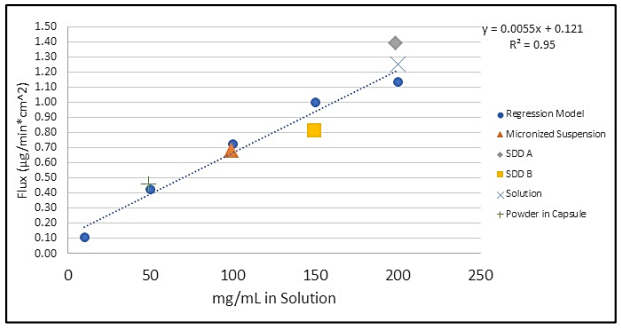

Table 1: Formulation Ranking and IVIVC Comparison

Formulation	In-Vitro Predictions Based on Flux and Permeability			% Agreement with In-vivo Results
	Flux (µg/min8cm^2)	Predicted AUC Rank Order (low -high)	Predicted Relative Change in AUC	
Native API (powder in Capsule)	0.465	1	NA	NA
Micronized Suspension	0.683	2	1.47	83.0
Spray Dried Dispersion A	1.394	5	3.00	130.5
Spray Dried Dispersion B	0.813	3/4	1.75	77.9
Solution (with Solubility Enhancers)	1.050		2.26	113.6

Formulation	In-Vivo PK Results			In-vivo Relative Change in AUC
	AUC (ng*hr/mL)	AUG 95% CI	Rank AUC Order (low-high)	
Native API (powder in Capsule)	93444	4327-182561	1	NA
Micronized Suspension	165381	87316-243447	2	1.77
Spray Dried Dispersion A	214736	172432-257039	5	2.30
Spray Dried Dispersion B	209784	182282-237287	4	2.25
Solution (with Solubility Enhancers)	185663	138719-232605	3	1.99

PRESENTOR BIOGRAPHY

Travis Webb is a Principal Scientist with the Product Development Group and has a Master of Science in Pharmaceutical Chemistry from the University of Florida and has worked in the pharmaceutical and biotech industry for 18 years, with a focus on oral and topical formulation and analytical development.

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INTRODUCTION

Oral bioavailability is a common problem in formulation development for BCS class II/III/IV compounds, which are also becoming more prevalent in the pharmaceutical landscape. The traditional methods for evaluating bioavailability enabling formulations has centered around increasing solubility and/or evaluating alteration in the dissolution profile via standard USP apparatus. However, it is well understood that there is a direct balance between solubility and permeability, and increasing the former does not necessarily increase the latter. In some cases the increase in solubility, especially using surfactants and colloid solutions, can effectively decrease the drug absorption. Further, for other compounds the rate limiting factor(s) may be a combination of solubility, dissolution rate, or permeability. Here we present a strategy utilizing dissolution and in-vitro permeability for formulation selection of a BCS class III compound.

EXPERIMENTAL

Dissolution Media: 3mM taurocholate, 0.75mM phospholipids, 148mM sodium, 106mM chloride, 29mM phosphates (FaSSIF).

Acceptor Media: 2% w/v Sodium Lauryl Sulfate Dodecahydrate in water

Dissolution Apparatus: Pion µFlux small volume side-by-side dissolution/flux apparatus.

PION Rainbow®: *In situ* fiberoptic probes with dedicated PDA (200-720nm) for each channel with 2mm stainless steel probes. Data collected at 240nm.

The kinetic dissolution, solubility, and permeability characteristics of a BCS Class III drug were evaluated in-vitro using a side-by-side flux cell. The donor chamber contained 20.0 mL of FaSSIF and the acceptor chamber was filled with 20.0 mL of SLS media to maintain pseudo-infinite sink conditions. The two chambers were separated by a biomimetic phospholipid barrier coated onto a PVDF membrane with a known surface area. The dissolution and flux for the compound was evaluated at 3 separate concentrations if micelle forming agents to increase the apparent solubility by increasing the bound fraction of dissolved drug. Separately several additional experiments (not presented here) were executed to evaluate the effects of the free fraction, particle size, and dose concentration on the steady state solubility and flux of the compound. From these studies 4 different formulations were screened and compared to the flux regression model in order to assess the possible relative changes in AUC compared to the early PK study "powder in capsule" formulation.

RESULTS

The results for micelle forming agents, surfactants, colloids, ext.., (fig. 1) demonstrated that increasing the apparent steady state solubility from ~38 µg/mL to ~57 µg/mL via the bound fraction had little to no impact on the effective flux of the API. Further studies ultimately indicated that the flux of the drug was improved by increasing the free fraction of dissolved drug and improving the dissolution rate (fig. 2). Based on these data a micronized suspension, two separate spray dried dispersions, and a solution formulation composed of water and orally acceptable organic solvents were tested and compared the flux to the permeability regression model developed based on the sum of the flux data (fig. 3) These formulations were also submitted for a single oral dose PK study. The results (table 1) for the in-vitro comparison were used to determine the rank order and predict the relative change in AUC compared to the reference formulation. These data indicated that SDD formulation A was most likely to result in the highest increase (~3X) in the AUC. SDD formulation B and the solution were predicted to be similar/the next highest at 1.8-2.5 fold increases in AUC. The results obtained from the in-vivo study were in good agreement with the predicted in-vitro results. The rank order of the formulation for AUC was confirmed in-vivo, and the predicted relative change in AUC was between ~75%-130% of the in-vitro results.

CONCLUSION

Biorelevant dissolution in combination with flux/permeability analysis can be an effective tool to identify characteristic properties as they relate to drug release and absorption in-vivo. While these type of studies cannot account for metabolic effects or efflux, they can be used in tandem with existing PK data to make better formulation selections and in some cases predictions for oral bioavailability.