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A Data Based Approach to Selection of Bioavailability Enhancement Strategy Using New Simultaneous Dissolution-Flow Through Permeability Cell for Formulation Development

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PURPOSE

To investigate a strategy for screening and estimation of bioavailability enhancement (BAE) for BCS class II, III, and IV drugs. The process uses in-vitro flux of formulated products through biomimetic membranes in conjunction with early phase pharmacokinetic (pk) data from the drug substance to predict relative changes to bioavailability and estimate the area under the curve (AUC) for proposed enhancing formulation(s).

Herein we describe the in-vitro permeability testing and results for selection of a BAE formulation for a new BCS class II/IV drug substance. Screening studies were performed using small volume side-by-side flux cells to evaluate candidate excipient/formulation options for improvements to in-vitro solubility and permeability. These data were used to select and prepare 3 test formulations, 1 oral suspension and 2 separate spray dried dispersions. The test formulations were evaluated for biorelevant solubility and permeability using a flow through flux cell apparatus in parallel with a USP dissolution bath and 200 mL vessels. These flux data were compared to the API in capsule permeability in conjunction with in-vivo pk data for the drug substance to predict relative changes in permeability and estimate the AUC for the new formulations. The test formulations were then submitted for a single dose animal pk study for confirmation and comparison to the in-vitro data.

OBJECTIVE(S)

To evaluate an in-vitro method for better predictions of bioavailability enhancement using existing in-vivo data from early phase animal or human pk studies.

METHOD(S)

Materials: *FaSSIF/FeSSIF* (Biorelevant.com), *Sodium Lauryl Sulfate-reagent grade* (VWR), *Poloxamer 407* (Sigma Aldrich), *Vit. E TPGS* (Parchem), *SilSol 6035* (Grace), *Kleptose Oral HP* (Roquette), *Polyvinylpyrrolidone (Alfa Aesar)*.

Donor media: 20 mL FaSSIF; Acceptor media 1% SLS.

µFlux (Pion) and Permetro (Logan) combined dissolution and flow through side-by-side diffusion cell apparatus. Diffusion barriers: PVDF membrane, GIT-0 Lipid solution (small scale) or Permeapad Barrier (full scale).

Detection: with in situ fiber optic probes with PDA (200-720 nm) with 2 mm stainless steel probes (Pion, Billerica MA).

Flux Testing: donor media-FaSSIF, acceptor media-1%SLS, temperature-37°C.

Sample Preparation: The silica dispersion was prepared by dissolving the API in acetone and then loading/drying onto the base in repeated intervals. All samples were dosed at 4 mg for the small-scale studies. Prototype formulation samples were prepared on the lab scale and dosed at 20 mg in HMPC capsules. Spray dried dispersion A (SDD) was prepared in acetone and methanol with HPMC-AS. SDD B was spray dried with HPMC. The micronized oral suspension was prepared using jet milled API dispersed in xanthan gum and poloxamer.

Analysis: Minitab® statistical processing software. Excipient screening samples were prepared as micro-blends.

RESULT(S)

The small-scale screening (**Table 1**) indicated a linear correlation between the steady state solubility (saturation) and in-vitro flux. These data also trended with the expected linear regression model for the free dissolved fraction of drug (**Figure 1**) which was developed during earlier studies. The results also suggested that the amorphous silica dispersion showed the best improvement. From the small-scale screenings, three formulations were selected to prepare as lab-scale prototypes (capsules), two spray dried dispersion (SDD) formulations and a micronized suspension. These formulations were evaluated for dissolution and flux using the Permetro flow through system to assess/verify the apparent improvements to the in-vitro flux from the small-scale screening carried through to the fully formulated drug product. The selection of the SDD approach was based on the results for the amorphous silica dispersion. However, spray drying is more scalable to a commercial process compared to the preparation of the silica dispersion. The micronized suspension was selected to investigate a ready made/pediatric acceptable liquid dosage form. The flow through in-vitro flux results for the 3 drug product formulations (**Table 2**) indicated that both of the SDD's improved the in-vitro permeability of the drug ~166-215% compared to the powder-in-capsule used in the phase one pk study. The suspension formulation also demonstrated a relative increase in permeability of ~ 32%. From these data it was hypothesized that SDD formulation A would likely result in the highest increase in bioavailability. However, both SDD formulations were expected to be similar.

The selected formulations were also submitted for single dose pk (dog) study. Using the results from the in-vitro studies, the regression model, and previous in-vivo pk data for the first trial powder in capsule formulation (**Table 3)**, the in-vivo AUC ranges were estimated for the new formulations. The span of the range was given by the 90% CI of the variance observed during the in-vitro testing. The in-vivo pk results (**Table 3)** confirmed that SDD A yielded the greatest increase in AUC compared to the powder-in-capsule (>200%), and SSD formulation B was only slightly less. The suspension also demonstrated an increased AUC of ~183%. The relative proportionality of the flux from the flow through cell was found to be similar to the relative AUC; and the percent agreement between the predicted and measured AUC for all three formulations was between 70%-100%.

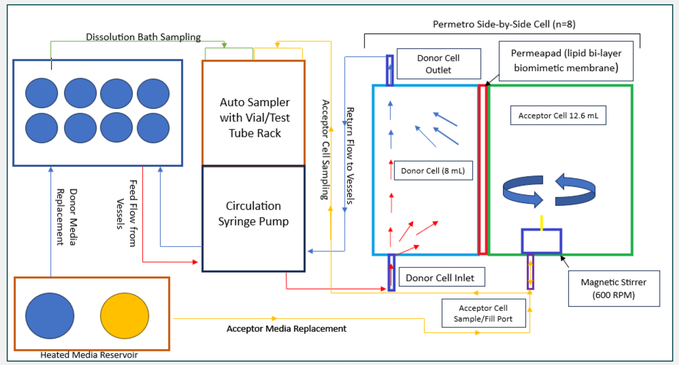

Figure 2: Permetro Side-by-Side Diffusion Cell Schematic

Enhancement Approach	Steady State Solubility (FaSSIF)	[µFLux] Flux (µg/min*cm^2	Relative Improvement in Permeability
Native API	~44-48 µg/mL	0.481	NA
Solubility Enhancing Dispersion (Poloxamer/TPGS)	~55-65 µg/mL	0.503	5%
Solubility Enhancing Dispersion (PVP)	~36-41 µg/mL	0.467	-3%
Solubility Enhanced Granulation (2-HP-B-CD)	~47-59 µg/mL	0.438	-9%
Micronized Suspension	~50-55 µg/mL	0.549	14%
Amorphous Silica Dispersion	90-100 µg/mL	0.645	34%

Table 1: Small scale In-vitro solubility and flux screening for bioavailability enhancement.

Formulation	Dosage Form	[Permetro] Flux (µg/min*cm^2)	% Increase Over Powder in Capsule
Native API	(pwd. in capsule)	~0.047	NA
Micronized Suspension	liquid	0.062	31.9
Spray Dried Dispersion A	capsule	0.101	114.9
Spray Dried Dispersion B	capsule	0.078	66.0

Table 2: Lab Scale In-vitro Permeability Formulation Screening

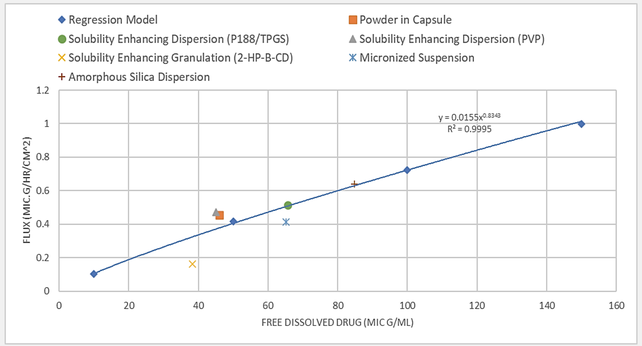

Figure 1: µFlux Comparison of small scale in-vitro flux results to the flux regression model for the API

Figure 3: Permetro Side-by-Side Diffusion Cell System with Dissolution Bath and Autosampler

CONCLUSION(S)

The proposed approach to in-vitro screening and formulation selection demonstrated both discrimination and selectivity based on the formulation changes. In-vitro modeling of the flux data with existing in-vivo pk data for the drug substance demonstrated the potential for accurate prediction/estimation of changes to the AUC and potential utility as a tool for formulation development and de-risking early-stage failures due to bioavailability problems.

Formulation	Predicted Range for AUC (ng*hr/mL)	Measured in-vivo AUC (ng*hr/mL) with 95% CI	% Agreement (IVIVC)
Powder in Capsule	NA	93444 (4327-182561)	NA
Micronized Suspension	112132-137051	171282 (78906-263658)	73%
Spray Dried Dispersion A	182668-223261	214736 (172432-257039)	95%
Spray Dried Dispersion B	141070-172419	209784 (182282-237287)	75%

Table 3: In-vivo AUC and IVIVC Correlation

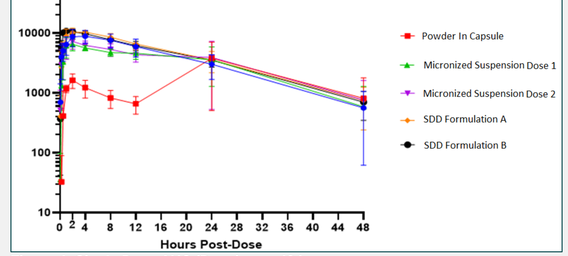

Figure 4: Single Dose AUC (Dogs) over 48 hrs.

REFERENCES

1: di Cagno M, Bibi HA, Bauer-Brandl A. New biomimetic barrier Permeapad™ for efficient investigation of passive permeability of drugs. Eur J Pharm Sci. 2015 Jun 20;73:29-34.

2: Bibi HA, Holm R, Bauer-Brandl A. Use of Permeapad® for prediction of buccal absorption: A comparison to in vitro, ex vivo and in vivo method. Eur J Pharm Sci. 2016 Oct 10;93:399-404.

3: Borbás E, Nagy ZK, Nagy B, Balogh A, Farkas B, Tsinman O, Tsinman K, Sinkó B. The effect of formulation additives on in vitro dissolution-absorption profile and in vivo bioavailability of telmisartan from brand and generic formulations. Eur J Pharm Sci. 2018 Mar 1;114:310-317.