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Using Biorelevant Flux Measurements for Prediction of Fraction Absorbed for the Drug Products of Poorly Soluble Compounds

Oksana Tsinman[1], Konstantin Tsinman[1], Enikő Borbás[2], Bálint Sinkó[1]

[1]Pion Inc., USA; [2]Budapest University of Technology and Economics, Hungary

CONTACT INFORMATION: ktsinman@pion-inc.com

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PURPOSE

It was demonstrated [1] that flux measurements provide more in-depth understanding of supersaturated systems than solute concentration measurements alone. Such measurements were further employed to characterize and explain the differences between brand name and generic drug products that were reported from the bioequivalence studies [2]. The benefits of flux measurements are based on the fact that they capture the complex interplay between effects of formulation ingredients on solubility, dissolution rate and permeability of an active pharmaceutical ingredient (API). From the other hand, there has not been a predictive model that would use flux measurements as an input parameter for calculation of maximum absorbable dose (MAD) or fraction of the API absorbed (Fa) from an oral dosage form. This study demonstrated a feasibility of using flux measurements through gastro-intestinal tract (GIT) mimicking artificial membrane to predict MAD and Fa values in biopharmaceutics modelling for BCS Class 2 drugs.

METHOD(S)

Formulations studied in this work:

Figure 1. Sporanox® solid dispersion commercial formulation of API Itraconazole (ITZ) (a), Micardis® (b), Actavis (c) and Sandoz formulations of API Telmisartan (TMS) used for the study.

Flux measurements through Double-Sink™ type PAMPA membrane [3] were performed using either µFLUX™ or MacroFLUX™ instruments (Pion Inc.) shown on Figure 2.

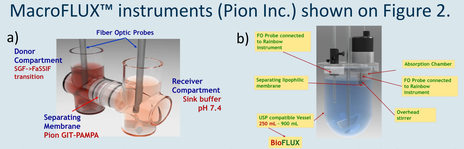


Figure 2. µFLUX device (a) uses volumes 16 – 20 mL in both donor and receiver chambers while MacroFLUX device has a receiver insert in either standard (1L) or shortened (500 mL) USP dissolution vessel.

Modelling Approach:

It has been shown [4] that fraction absorbed (F_a) under quasi steady-state assumptions can be expressed through unitless parameters – dissolution number (D_n), dose number (D_0) and permeation number (P_n):

$$F_a \approx 1-\exp\left(-\frac{1}{\frac{1}{D_n}+\frac{D_0}{P_n}}\right) \qquad (1)$$

RESULT(S)

For Solubility-Permeability absorption limiting cases fraction absorbed (Fa) can be expressed through flux (J):

$$F_a = \frac{P_n}{D_0} = \frac{J\cdot(A_{SI}/V_{SI})\cdot T_{transit}}{m_{Dose}/V_{SI}} \qquad (2)$$

where area to volume ratio of small intestine (SI): $A_{SI}/V_{SI}\sim 2/r_{SI}$, m_{Dose} is a dose weight (mg), transit time $T_{transit}$ ~ 210 min and radius of SI r_{SI} ~ 1.5 cm [4].

Itraconazole Formulations

Recent publication [5] demonstrated that flux measurements can be used to rank order ITZ formulations in relation to in vivo PK (AUC) data (Figure 3):

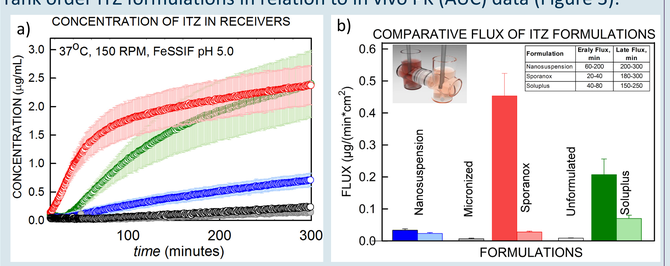


Figure 3. Concentration of ITZ in receiver chamber of µFLUX device as a function of time (a) and flux calculated at different time intervals (b) for Sporanox® (red), Soluplus® ASD (green), nanocrystalline ITZ (blue), micronized ITZ (grey) and untreated crystalline ITZ (white).

Using Eq. (2) the fraction absorbed for Sporanox® assuming the initial flux would sustain *in vivo* would be:

$$Sporanox: F_a(\max) = \frac{0.00045\cdot 1.33\cdot 210}{0.4} * 100\% = 43\%$$

(Flux mg·min-1 ·cm-2; A/V, cm-1; Transit Time, min; Dose(mg)/ 250mL)

The fraction absorbed for ITZ was reported to be **85%** which is in a reasonable agreement with an estimate that uses the data from a simple *in vitro* assay. The transit time 210 min can be underestimated for ITZ that shows T_{max} ~ 5 hours in human *in vivo* studies.

Telmisartan Formulations

Application of MacroFLUX to compare various generic formulations of Telmisartan with reference product (Micardis®) was reported recently [2]. It was demonstrated that a risk factor in bioequivalence studies can be predicted from flux measurements.

In this study a modified device named **BioFLUX** that allows working with biorelevant **250 mL** volumes was used (Figure 4).

Figure 4. Differences between MacroFLUX and BioFLUX setup.

All formulations of TMS precipitated in the dissolution compartment after conversion of 200 mL of SGF to 250 mL of FaSSIF at 30 min. This affected the flux measured after about 60 min of the experiment, see Figure 5.

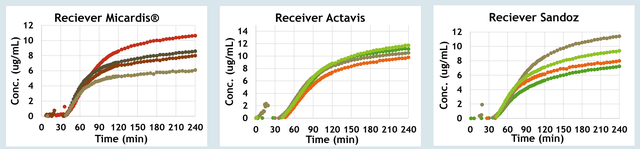


Figure 5. Concentration of TMS in receiver chamber of BioFLUX device as a function of time (a) Micardis®, (b) Actavis and (c) Sandoz. Four curves represent four replicates of the measurements.

It must be noted that no precipitation of TMS was observed during the study [2] when the drug products were dissolving in in 850 mL of SGF then converted to 1062.5 mL of FaSSIF after 30 min.

Thus, TMS formulations seem to be sensitive to the supersaturation ratio and future research will be directed towards considering precipitation as a part of the model.

Table 1 below summarize the initial flux values and predicted fraction absorbed for studied formulations.

Table 1. Initial flux values and predicted fraction absorbed for drug products used in this study.

Drug Product	Initial Flux, µg·cm^{-2}·min^{-1}	Ratio to Micardis	Predicted F_a	Reported F_a
Micardis (TMS, 40 mg) BioFLUX, 250 mL	0.80 (0.12)	1.0	~100%	90%
Micardis (TMS, 40 mg) MacroFLUX, 1062.5 mL [2]	0.31 (0.01)	1.0	54%	90%
Actavis (TMS, 40 mg) BioFLUX, 250 mL	0.67 (0.05)	0.84	~100%	90%
Actavis (TMS, 40 mg) MacroFLUX, 1062.5 mL [2]	0.24 (0.01)	0.77	42%	90%
Sandoz (TMS, 40 mg) BioFLUX, 250 mL	0.66 (0.08)	0.83	~100%	90%
Sporanox (ITZ, 8 mg) µFLUX, 20 mL	0.45 (0.07)	N/A	45%	85%

CONCLUSION(S)

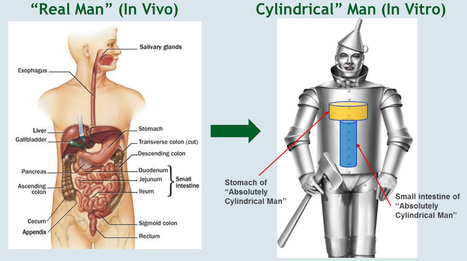
The feasibility study demonstrated that flux values measured under the biorelevant conditions could be used as input parameters for biopharmaceutics modelling and simulations.

BioFLUX data predicted the differences in C_{max} for Telmisartan formulations based on the differences in initial flux.

The flux measurements capture the influence of formulations on all key physicochemical parameters affecting oral absorption.

A follow up investigation is setup to validate and augment this approach by comparing predicted Fa based on in vitro flux results to the reported in vivo Fa values for a larger set of drugs.

Cartoon Depiction of the Approach of this Study



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