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Prediction of Maximum Absorbable Dose and Fraction Absorbed based on in vitro Flux Measurements

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PURPOSE

Utility of ***in vitro* flux measurements** in formulation development and bioequivalence prediction have been explored in a number of recent studies [1 - 3]. The benefits of such 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). This work extends usage of flux values for predictive biopharmaceutics modelling, namely by using them as input parameter for calculation of **maximum absorbable dose** (MAD) or **fraction absorbed** (F_a) for an oral dosage form. This study explores 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)

Drug Products

API	pK_a	Solubility in FaSSIF, µg/mL	Drug Product	Dose, mg
Itraconazole (ITRA)	3.9(B)	< 0.1	Sporanox® Capsule	100
			Sporanox® Solution	100
			SUBA-ITRA	50
Albendazole ABZ	10.3(A) 4.2(B)	1.9	Albendazole	200
Carbamazepine CBZ	N/A	320	IR	200
			CR	400

Flux Measurements

BioFLUX™ device was used for flux measurements. The schematic of the experiments is shown on Figure 1. Concentration in both chambers were monitored in real time using *in situ* fiber optic dip probes connected to the Rainbow instrument (Pion Inc.).

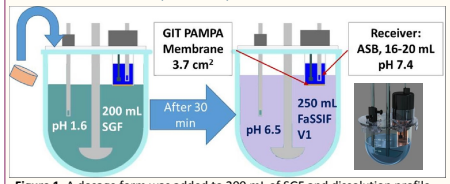

Figure 1. A dosage form was added to 200 mL of SGF and dissolution profile was monitored. After 30 min medium was changed to 250 mL of FaSSIF continuing the concentration monitoring in both dissolution and receiver chambers. An insert shows BioFLUX™device.

RESULTS

Modelling Approach

Flux through Double-Sink™ PAMPA [4] membrane (DS PAMPA) was calculated based on concentration – time profiles in the receiver chamber

$$J_{invitro} = \frac{1}{A} \cdot \frac{dm}{dt} \quad (1)$$

where A is the area of the membrane in the BioFLUX™ device and dm/dt (µg/min) is the rate of absorption into receiver chamber.

It can be shown [5] that fraction of orally absorbed drug (F_a) for solubility-permeability limiting cases can be expressed through trans-membrane flux (J_{invivo}):

$$F_a = \frac{J_{invivo} \cdot (A_{SI}/V_{SI}) \cdot T_{transit}}{m_{Dose}/V_{SI}} \quad (2)$$

where area to volume ratio of small intestine (SI) A_{SI}/V_{SI}, m_{Dose} is a dose weight (mg), V_{SI} is volume of small intestine and $T_{transit}$ is transit time.

Taking advantage that effective permeability P_e values measured with DS PAMPA linearly correlated with human jejunum permeability P_{HJ} with linear coefficient ~ 1 and intercept ~ 0 [4]:

$$F_a \approx \frac{J_{in\,vitro} \cdot (2/r_{SI}) \cdot T_{transit}}{m_{Dose}/250} \quad (3)$$

where radius of SI r_{SI} ≈1.5 cm and volume of SI assumed to be 250 mL.

Itraconazole Formulations

Dissolution data (SGF only) and concentration – time profile in the absorption chamber for studied ITZ products presented in Figure 2 [6]:

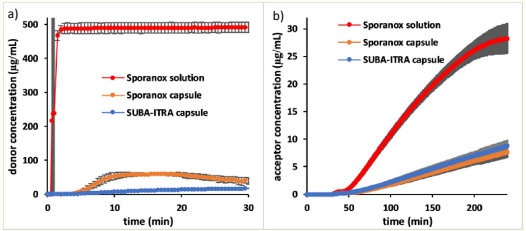

Figure 2. Dissolution in SGF (a) and appearance profile (b) of ITRA from Sporanox solution (100 mg), Sporanox capsule (100 mg) and SUBA-ITRA capsule (50 mg).

While concentration-time profile in FaSSIF could not be measured due to extreme turbidity, the absorption profile of ITZ for this phase of experiment demonstrated superior flux of Sporanox solution comparing to capsule formulations. Figure 3, a shows flux values calculated based on the 60 -120 min slope of concentration-time profile of Figure 2, b, while predicted based on Eq. (3) F_a values are shown on Figure 4, b.

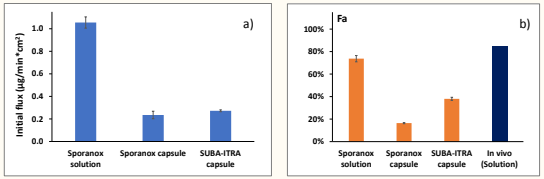

Figure 3. Initial flux of ITRA formulations measured in the receiver chamber after conversion of the donor to FaSSIF (a). Predicted fraction absorbed (orange bars) for corresponding dosage forms in fasted state (b). Blue bar represents reported human fraction absorbed from orally administered solution [5].

Albendazole Formulation

ABZ is quickly reached a plateau of 200 µg/mL (~ 20% dissolved) in SGF. Its concentration decreased significantly upon switching media to FaSSIF (Figure 4, a). However, apparent concentration in donor remained ~ 25 times higher than thermodynamic solubility of ABZ in FaSSIF (Table 1).

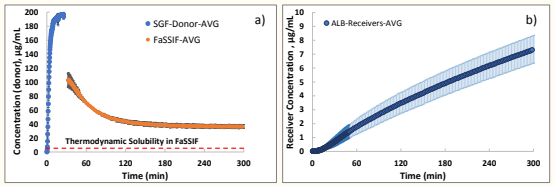

Figure 4. Concentration of ABZ in donor (a) and receiver chamber (b). Orange dots (a) represent "apparent" concentration of ABZ as spectral shift characteristic of forming nanoparticulate phase was detected.

Further investigation of this phenomenon revealed that ABZ formed second nanoparticulate phase upon SGF – FaSSIF transition that could be detected by a spectral shift evident in the derivative spectral analysis (Figure 5). Zero Intercept Method (ZIM) analysis (Figure 6) confirmed ABZ kinetic solubility of ~ 28 µg/mL. Flux of ABZ changed from 0.16±0.03 to 0.08±0.01 µg cm^{-2} min^{-1}. Estimation of Fa based on initial flux from 200 mg dose gave 5.6%. Reported human Fa from 1400 mg dose was 2.7% [5].

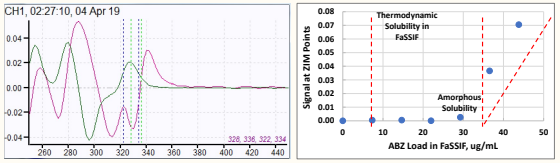

Figure 5. ABZ 2nd derivative absorbance in FaSSIF (pink) versus standard (green) of ABZ by ZIM method. **Figure 6**. Determining amorphous solubility indicating presence of nano phase.

Carbamazepine Formulations

Immediate release (IR) and controlled release (CR) formulations of CBZ were used in the study (Figure 7).

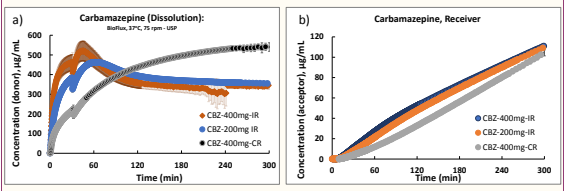

Figure 7. Dissolution/precipitation (a) and absorption (b) profiles for IR and CR forms of CBZ.

Despite of the significant difference in the dissolution behavior between 200 and 400 mg doses of IR product (Figure 7a), there was almost no difference in the flux (Figure 7b). CR product does not go through re-precipitation phase (Figure 7a) with its flux reaching its maximum at ~ 4 – 5 hrs (Figure 7b).

CONCLUSION(S)

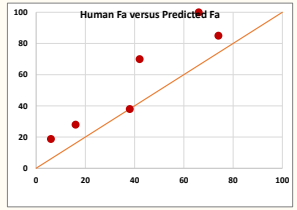

Figure 8. In vivo F_a versus flux-based predicted values. Unity line is added for convenience.

Human F_a for BCS Class 2 compounds can be reasonably **estimated based on** the in vitro **flux** measurements under biorelevant conditions (Figure 8).

Flux values measured under the biorelevant conditions *in vitro* could be used as input parameters for **biopharmaceutics modelling**.

A single **flux** experiment can replace a series of measurements by **capturing** drug product specific **interplay between solubility, dissolution rate and permeability**.

REFERENCES

1. Raina S, et al. J. Pharm. Sci., 2014, 103 (9), 2736.
2. Borbás E, et al. Eur J Pharm Sci. 2018;114:310.
3. Tsinman K, et al. Pharm Res. 2018;35(8) : 161.
4. Avdeef A, et al. J Pharm Sci. 2007 Nov;96(11):2893.
5. Sugano K. Biopharmaceutics Modeling and Simulations. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2012. 515 p.
6. Borbás E, et al. Mol. Pharmaceutics 2019, 16 (10): 4121.

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