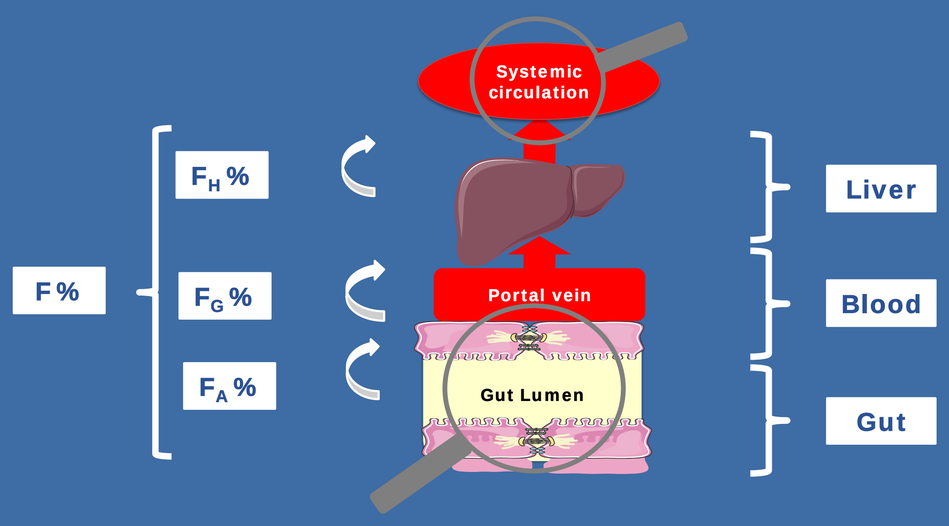
In vitro prediction of the performance or equivalence, of different formulations of the same drug substance using a 3D reconstructed human intestinal tissue model: application to generics or drugs in development

Oroxcell, Romainville, France
E-mail: rola.barcham@oroxcell.com

R. Barcham, C. Dini

Background

- "The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to reduce the need for *in vivo* bioequivalence studies in Human, in order to lower costs of development, increase the market access for generic drugs and from an ethical point of view, avoid unnecessary exposure of healthy volunteers (Humans).
- These waivers are limited to Class I and Class III drug products, only.
- If the Caco-2 cells, remain the *in vitro* gold standard to estimate the absorbed fraction (F_A%) of Drug Substance, unfortunately, they cannot be used to evaluate the performance of Drug Products, due to an over sensitivity to excipients.
- On the contrary, the 3D organotypic human model (EpiIntestinal tissue model), which should theoretically provide access to [FA% x FG%] of a Drug Substance thanks to a metabolic activity comparable to that of the human intestine, has been found, in our hands, to be much less sensitive to excipients, even at high concentrations.
- For that latter reason, we have decided to explore this 3D organotypic Human model in the view of assessing Drugs Apparent permeability in different formulations.



Objectives

- Demonstrate that a 3D organotypic Human Model would be eligible to elaborate a correlation curve according to BCS-based biowaivers.
- Demonstrate the feasibility to testing various formulations of a same drug substance in order to determine the impact of formulations upon drug apparent permeability.
- Investigate if the model would predict the bioequivalence of forms in case of paediatric or generic forms

Test system : 3D organotypic Human EpiIntestinal tissue model

- Cells origin : Jejunum biopsy from Human donors.
- Cultivated at Air-liquid-interface
- Incorporates Enterocytes, Paneth-, Goblet-, M-, Cup-, Tuft-cells and produces mucin.
- Exchange surface of 20 to 30 bigger than Caco-2 cells (microvilli , villi, crypts, foldings)
- Display of a barrier function, efflux transporters and metabolism enzymes

Study design

First of all, we have pre-qualified the 3D organotypic Human Model, not only through its biological composition, but also for its ADME properties, such as permeability capacity to discriminate between low to high permeable drugs, presence of efflux transporters, presence of metabolic enzymes.

- Step 1 : Preliminary establishment of a Correlation Curve using prototypal drugs of known Absorbed Fraction in Human
- Step 2 : Demonstration of the impact of formulations over drug permeability
  - Determination of Intrinsic Drug Substance A permeabilities with Caco-2 and EpiIntestinal tissue model, and results comparison
  - Assessment of Drug A permeability in its formulation on EpiIntestinal tissue model and in the intended condition of use (BCS conditions).
  - Comparison of permeabilities of several Drug Products (P1 to P5) of the same Drug A to determine the impact of their respective formulation on drug permeability
- Step 3 : Comparison of different adult and paediatric forms of vigabatrin for their impact on the absorption of the active substance vigabatrin
  - Investigation for the equivalence of the paediatric Kigabeq® (infantile 500 mg soluble tablet form) to the reference medicine Sabril® (500 mg granule form).

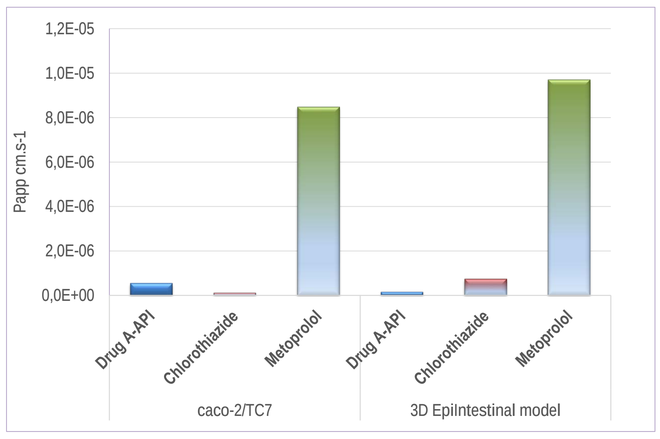
Results

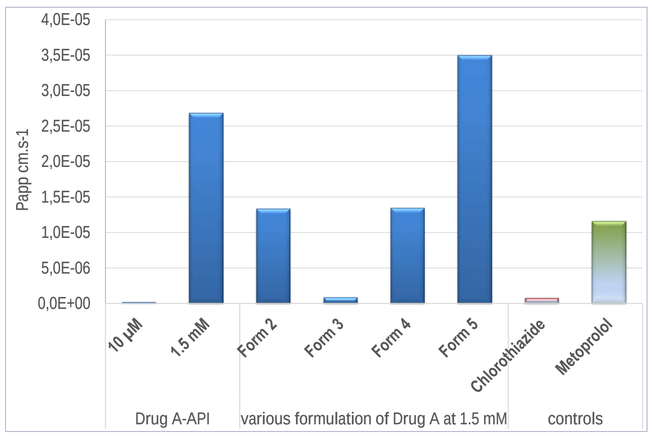
❖ STEP 1 - Drug permeation: comparison of the apparent permeability coefficients (Papp) in the EpiIntestinal model *with* historical absorbed fractions in Human (Fa%)

Test compound	Mean Papp A-B (10^{-6}cm/s)	Log Mean Papp	Predicted Fa%	Human Fa % (Lit.)	Permeability group
Caffeine	15.1	-4.82	96.1	100	High
Metoprolol	9.70	-5.01	93.2	95	
Propranolol	8.38	-5.08	91.9	90	
Sulfadiazine	7.14	-5.15	90.2	85	
Tolbutamide	17.3	-4.76	96.7	85	
Amiloride	0.52	-6.29	31.6	50	Moderate
Atenolol	0.54	-6.27	32.6	50	
Famotidine	0.50	-6.30	31.0	38	Low
Chlorothiazide	0.74	-6.13	40.4	36	
Amdinocillin	0.24	-6.62	17.7	10	
Xamoterol	0.31	-6.51	21.6	9	
Ganciclovir	0.46	-6.34	29.3	9	
Lucifer yellow	0.03	-7.52	3.1	0	Zero

❖ STEP 2 - Evaluation of absorption promotion: comparison of Drug Substance vs. Drug Product Apparent permeabilities

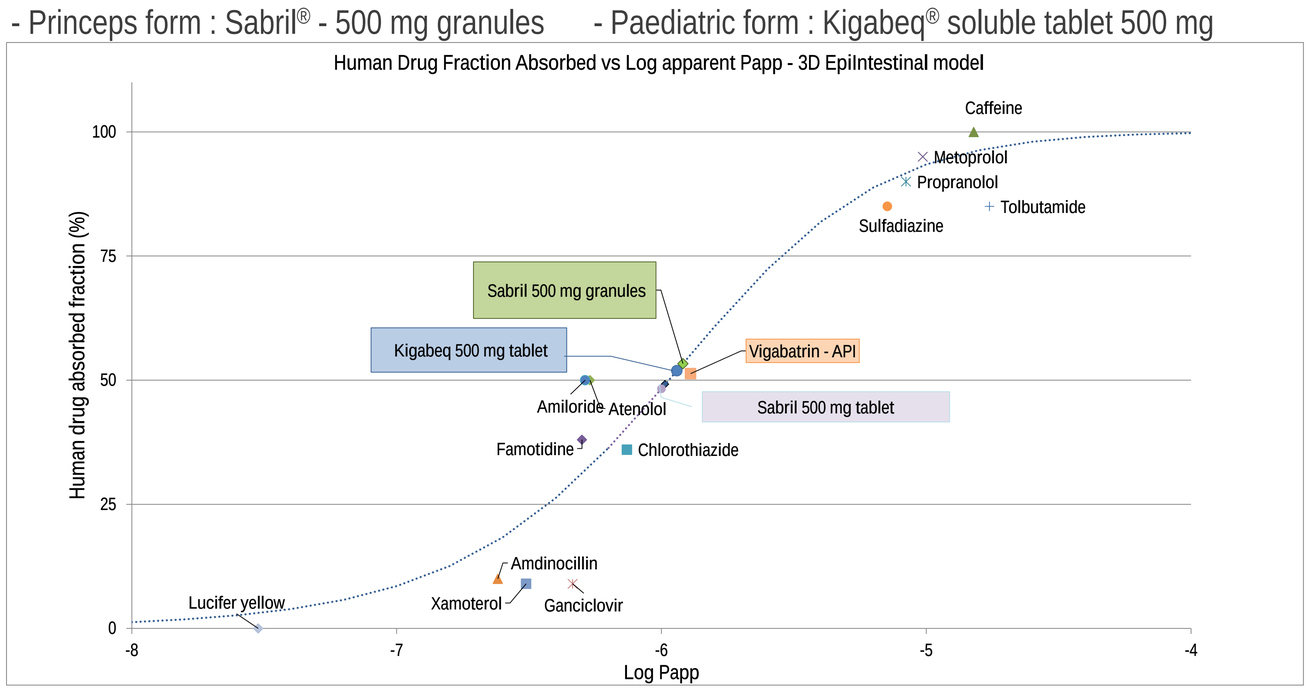
- Comparison of the intrinsic permeability of Drug Substance A at 10 µM, in Caco-2/TC7 *vs* 3D intestinal Model
- Influence of the formulation of Drug Substance A (3D Model)





❖ STEP 3 : Comparison of different vigabatrin medicine (adult and paediatric forms), for their equivalence in Drug Permeability using a BCS like correlation curve

- Active ingredient : Vigabatrin
- Princeps form : Sabril® - 500 mg granules
- Adult form : Sabril® - 500 mg tablets
- Paediatric form : Kigabeq® soluble tablet 500 mg



- ➢ All test items were tested at the same concentration (500 mg in 250 ml)
- ➢ Estimated absorbed fraction of vigabatrin in Human 50-60% according to literature
- ➢ The predicted Fa% for vigabatrin was determined at 51% using the 3D intestinal model
- ➢ The predicted Fa% for formulated vigabatrin ranged from 49% to 53%

Conclusions

❖ Our data suggest that the 3D organotypic Human EpiIntestinal tissue model, can be considered as a suitable model for performing BCS-biowaiver based strategies, on one hand, and to address the impact of formulations upon the drug product absorption on the other hand, knowing that this latter potential effect is hardly been addressed with currently available *in vitro* models.

❖ Both paediatric and adult forms of vigabatrin showed no significant impact on its absorption.

❖ Retrospective *in vitro* study perform with 3D models classified both Kigabeq® (paediatric form) and Sabril® adult tablet form as equivalent to the reference medicine Sabril® (500 mg granules) in terms of absorption.