Integrating bioaccessibility data from the SurroGUT™ tiny-TIM*sg* advanced *in vitro* gastrointestinal model into a physiologically based biopharmaceutics model (PBBM) of a BCS class IV compound to predict pharmacokinetic (PK) performance

Vanessa Mancini, Bohan Hu, Connor O'Farrell

InnoGI Technologies, Delft, The Netherlands

E: vanessa.mancini@innogitechnologies.com

Introduction

The aim of this study was to develop and implement a PBBM to predict the human PK behavior of an orally administered BCS IV drug (compound X) under fasted conditions. The advanced tiny-TIM*sg* gastrointestinal model, part of the SurroGUT™ platform, was used to model drug release, dissolution and passive absorption *in vitro*. The resulting bioaccessibility profile was integrated into the PBBM using GastroPlus®.

Learning Objective

A PBBM was successfully developed for oral administration of a BCS Class IV compound under fasted state conditions. Guided by *in vitro* bioaccessibility data from tiny-TIM*sg*, the human PK performance was accurately predicted. Tiny-TIM*sg* bioaccessibility data may be a valuable input to PBBM platforms to improve predictivity of *in silico* models.

Methods

A three-compartmental PK model was developed for compound X using GastroPlus® (v9.9, Simulations Plus). PK parameters were derived from a healthy adult population. The distribution and elimination model was verified using previously published intravenous (IV) mass balance data. Drug release, dissolution and passive absorption were modelled in tiny-TIM*sg*, a dynamic, computer-controlled, two-compartmental *in vitro* model of the stomach and small intestine (SI) (**Figure 1**). A clinically relevant dose of the compound was administered to the stomach compartment with 240 mL water. Media saturated with dissolved drug passed through a filtration unit, located at the end of the SI compartment and was collected at predefined time intervals. The fraction of drug present in the filtrate is referred to as bioaccessible.

The tiny-TIM*sg* bioaccessibility profile was imported to GastroPlus® as an absorption profile, following specific modifications of the dissolution and advanced compartmental absorption and transit (ACAT) models.

Figure 1. Tiny-TIM*sg* equipped with the (A) advanced gastric compartment, (B) small intestinal compartment, and (C) filtration system.

Results

The total bioaccessibility from the small intestinal compartment under fasted conditions was 7.9 ± 1.8% (n=2) of the total recovered drug (**Figure 2A**). Guided by the tiny-TIMsg bioaccessibility profile, the PBBM accurately predicted the fasted state PK profile (**Figure 2B**), with predicted to observed ratios of C_{max}, t_{max} and AUC of 1.09, 1.25 and 0.7, respectively.

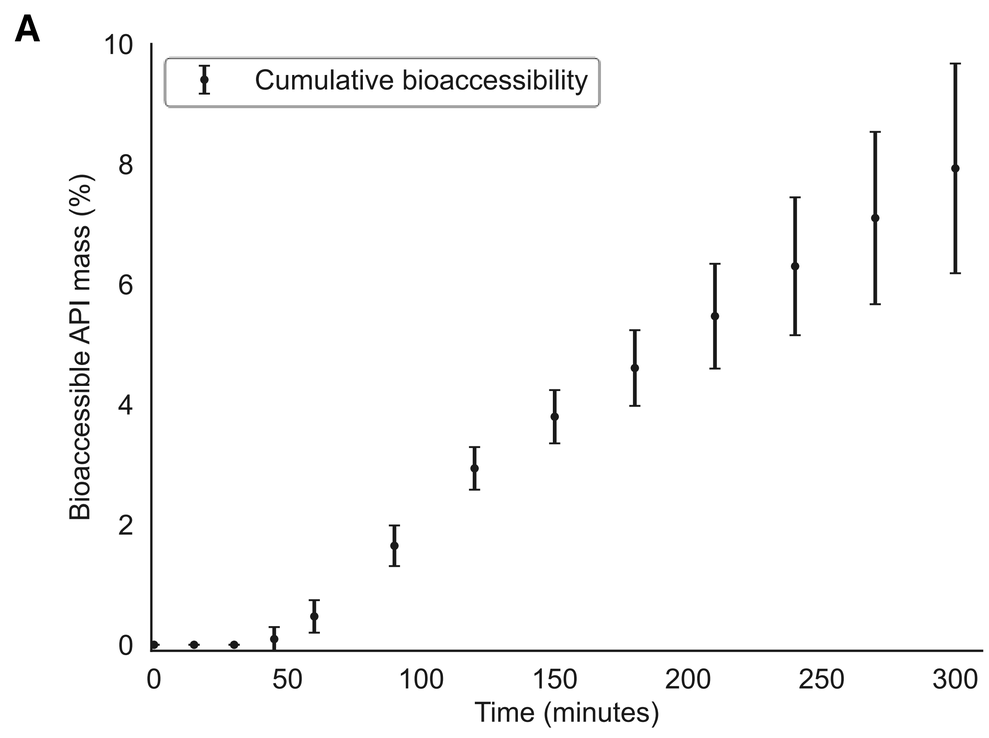

Figure 2. **A)** Cumulative bioaccessibility profile of compound A from an oral dosage form under fasted conditions in tiny-TIMsg (% of recovery, average ± stdevp, n=2). **B)** Prediction of plasma concentration of compound X following oral administration of a single oral dose to healthy human adults in the fasted state. Observed data is presented as mean ± standard deviation.

Conclusion

Bioaccessibility results from tiny-TIM*sg* were integrated into GastroPlus® to predict clinical PK observations with success. The SurroGUT PBBM was able to capture the PK profile and predict key PK parameters C_{max}, t_{max} and AUC within 1.3-fold. The combination of tiny-TIMsg in vitro data and GastroPlus® may be a valuable tool in the growing array of PBBM approaches for modelling gastrointestinal luminal and PK phenomena of challenging BCS IV compounds.

References

- Barker, R. et al., J. Pharm. Sci. 2014, 103 (11), 3704−3712.Bellmann, S., et al., Food Res. Internat., 2016, 88: 191-198.
- Dickinson, P.A., et al., 2012. The AAPS Journal 14 (2), 196–205.
- Luo, L. et al, 2022 AAPS PharmSciTech 23:185