A Novel Physiologically-Based Mechanistic Model for Predicting Oral Drug Absorption: The Advanced Dissolution, Absorption, and Metabolism (ADAM) Model

M. Jamei[1], J. Yang[1], D. Turner[1], K. R. Yeo[1], G. T. Tucker[1,2], and A. Rostami-Hodjegan[1,2]

M.Jamei@Simcyp.com

1- Simcyp Ltd, Blades Enterprise Centre, John St, Sheffield, S2 4SU, UK
2- Academic Unit of Clinical Pharmacology, University of Sheffield, Sheffield, UK

Objectives

(1) To use the ADAM model to predict first-pass intestinal extraction (E_G) and its *inter-individual variability* in humans.

(2) To assess the sensitivity of predictions to the distribution of CYP 3A in the gut (Paine *et al.* 2006).

The ADAM Model

The Advanced Dissolution, Absorption and Metabolism (ADAM) model, as implemented in Simcyp© Version 7, predicts the rates and extents of intestinal drug absorption and metabolism and their associated inter-individual variability.

The model is a population-based mechanistic representation which accounts for the *heterogeneity of the gastrointestinal tract* and considers the processes of dissolution, regio-specific gastrointestinal fluid dynamics, gut wall permeability and gut wall degradation and metabolism, with implicit consideration of active transport.

Physiological factors considered include:

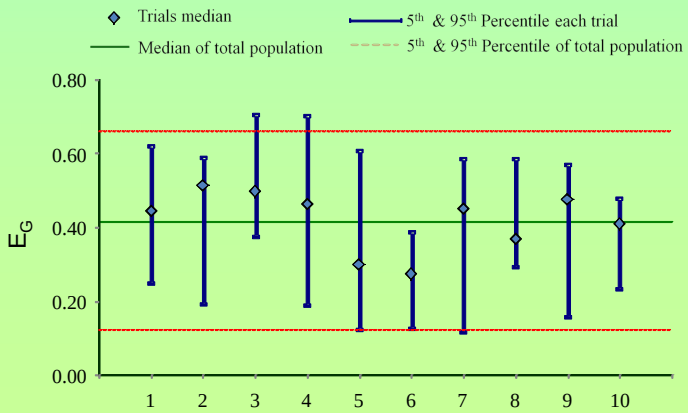
- Gastric emptying,
- GI tract surface area,
- Intestinal transit time,
- Luminal pH effects,
- The heterogeneous distribution of enterocytic blood flow,
- The heterogeneous distribution of CYP enzymes in the gut wall.

The generalised diffusion model of Wang and Flanagan (1999) is implemented. This extends the Hixson-Crowell and Higuchi-Hiestand dissolution models, and describes dissolution under both sink and non-sink conditions.

Food effects, including the impact of changes in gastric emptying, splanchnic blood flow and luminal pH, are also simulated.

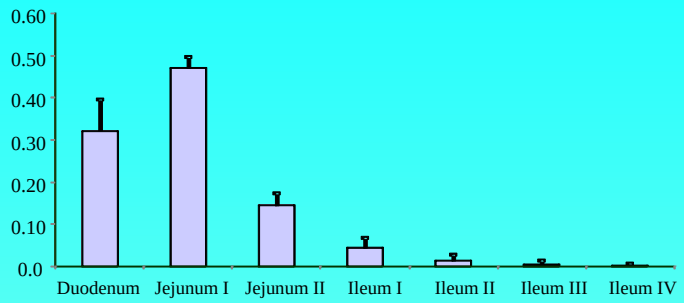
A Case Study

Physiochemical and *in vitro* data on midazolam collated from the literature were entered into the ADAM model to predict its first-pass intestinal extraction ratio (E_G) in 4 males and 1 female (age 18 to 51 years) enrolled in 10 virtual trials. The predicted mean E_G value (0.40 ± 0.17 SD) was similar to that determined experimentally in anhepatic patients (0.43 ± 0.18 SD) by Paine *et al.* (1996). The observed variability in E_G (0.14 to 0.59) was also predicted well by the simulation.

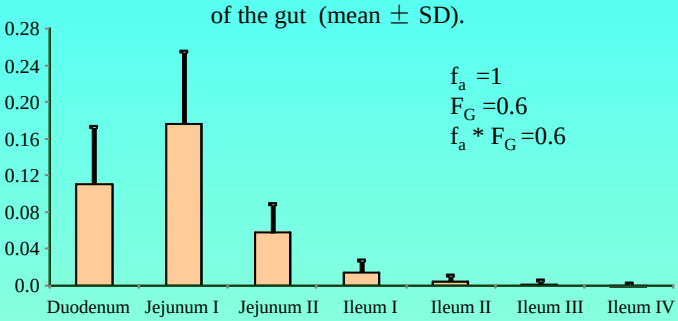


Prediction of the E_G of midazolam and its variability in 10 groups of 5 individuals selected randomly from a population of 50 virtual subjects.

The ADAM model outputs regional fractions of the dose absorbed and metabolised in different segments of the gut. The results indicate that the absorption of midazolam is not solubility-limited, and that the dose is completely absorbed.

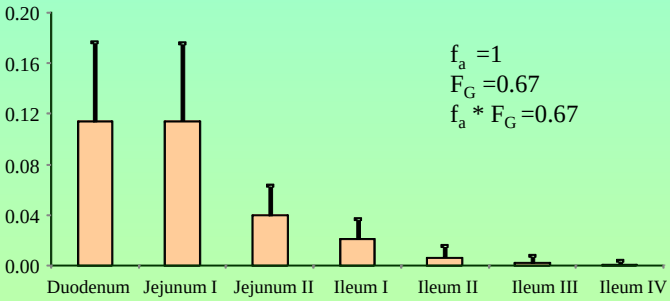


Fraction of dose absorbed from different segments of the gut (mean ± SD).



Fraction of dose metabolised in different segments of the gut (mean ± SD).

The simulation was repeated assuming an even distribution of CYP 3A along the small intestine. The pattern of regional absorption of midazolam was unchanged but the predicted mean value of E_G decreased to 0.33.



Fraction of dose metabolised in different segments of the gut, assuming an even distribution of CYP 3A.

Conclusions

The ADAM model is capable of predicting spatial and inter-individual variability in intestinal drug absorption and metabolism along the gut. Its use exemplifies the value of physiologically-based mechanistic models, with incorporation of realistic population variability, in the drug development process.

References

Paine MF, *et al.* (1996) *Clin Pharmacol Ther* **60**:14-24.
Paine MF, *et al.* (2006) *Drug Metab Dispos* **34**:880-886.
Wang J and Flanagan DR (1999) *J Pharm Sci* **88**:731-738.