Bringing physiologically-based pharmacokinetic (PBPK) simulation to early drug discovery and development

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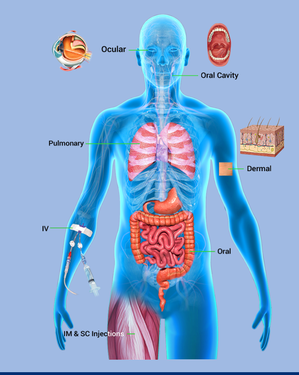

Summary

Lack of efficacy continues to be a problem in drug development. Piecemeal rules of thumb such as Lipinski's Rule of Five [1] help avoid compounds likely to be poorly absorbed, but many otherwise "allowed" property combinations can also lead to problems.

Good and bad interactions can be identified using physiologically-based pharmacokinetic (PBPK) simulation programs like GastroPlus™. Such programs are used to analyze pre-clinical and clinical data, and so have to be able to take variations in subject sex, weight, and disease state into account. They also need to incorporate subtle transporter and metabolic effects. Such details are less relevant in discovery and lead optimization, where the goal is to quickly survey likely problems with a class of chemistry and to differentiate them from ones that are specific to a particular compounds. Rodent PK is especially relevant early on.

We have created a streamlined, high-throughput version of the GastroPlus gastrointestinal absorption model for ADMET Predictor™ that enables users to rapidly estimate percentage absorbed (%Fa) and percentage available after first-pass metabolism (%Fb) for a typical rat or human subject (Figures 1 & 2).

Experimental property values can be used if available, but the validation results shown here were obtained using only *in silico* property predictions from ADMET Predictor. Experimental deviations from those predictions can provide important insight into complicating factors that are best addressed early in a project.

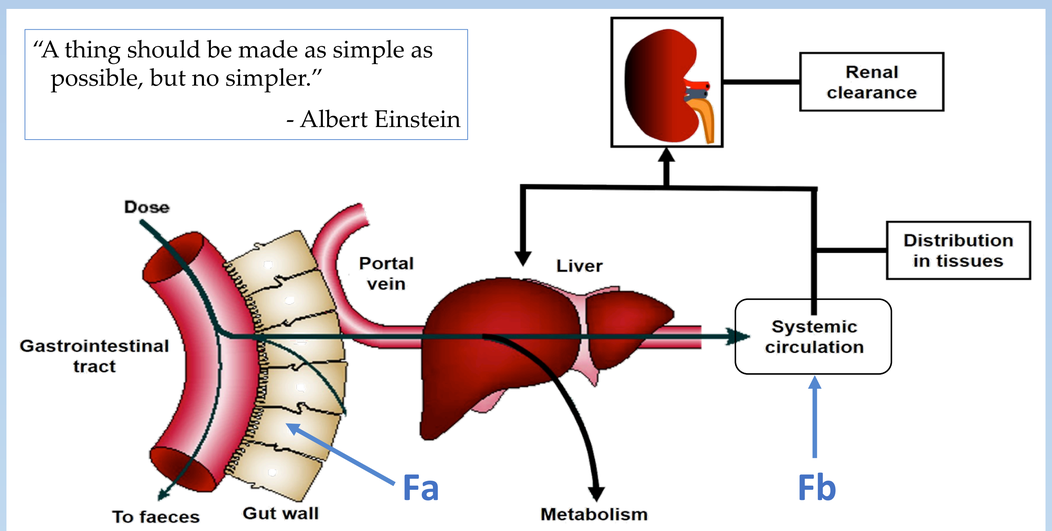

Figure 1: Simple schematic overview of the high-throughput pharmacokinetic system included in the HTPK Simulations Module of ADMET Predictor. QSAR models are available for predicting key PK parameters for rats and human beings, including water solubility, pKa, logP, fraction unbound in plasma (fup), blood:plasma ratio (RBP), microsomal binding (fumic) and liver microsomal intrinsic clearance (HLM and RLM CLint). Mechanistic models for volumes of distribution are available for rats and humans, as is a statistical model for human Vd.

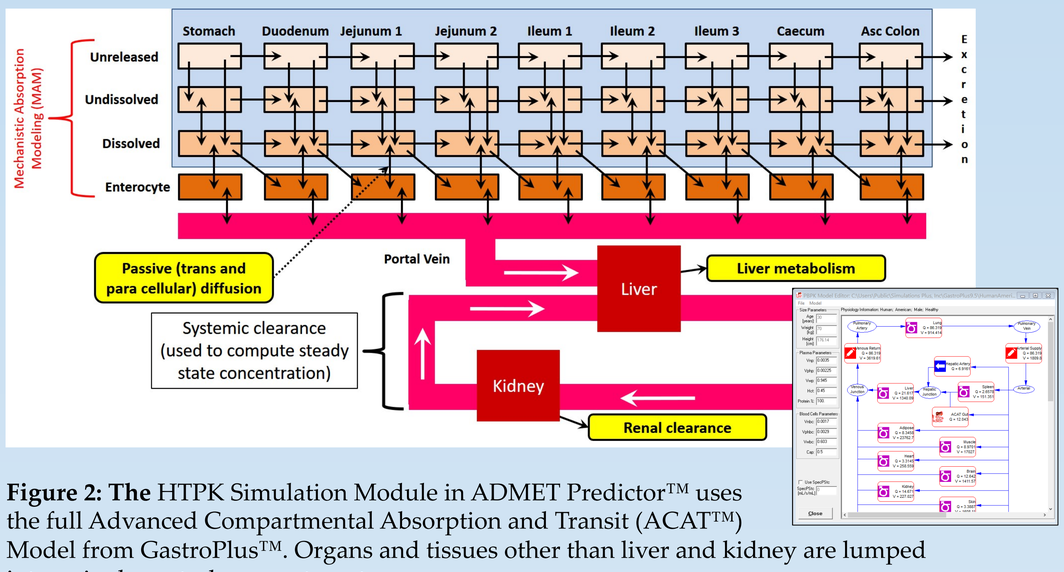

Figure 2: The HTPK Simulation Module in ADMET Predictor™ uses the full Advanced Compartmental Absorption and Transit (ACAT™) Model from GastroPlus™. Organs and tissues other than liver and kidney are lumped into a single central compartment.

Caveats

- The dose is treated as an immediate release tablet. No attempt is made to accommodate the specific physical state represented by gavage. In practice, the material delivered by gavage to rats can be a slurry, a suspension, an emulsion or a true solution. Which it is depends on the chemistry involved and the business practices of the company or institution.
- Any precipitate is presumed to have the same particle size as the original dosage form. The particle size is 25 μm by default but can be adjusted.
- ADMET Predictor has QSAR models for predicting oxidation mediated by rat and human microsomal cytochrome P450s (CYPs). Glucuronidation is not accounted for quantitatively, nor are plasma or esterase activities.
- No provision is made for enterohepatic circulation (EHC) or biliary excretion.
- Only fasted adult male rat and human physiologies are currently supported.

Validation Results

The simulation model has been validated in several ways. Among others:

- The simplified high-throughput simulation model in ADMET Predictor produces absorption and bioavailability estimates very close to those from GastroPlus when run using the same PK property estimates (Figure 3).
- Most predicted absorption and bioavailability values for humans lie within 2-fold of literature values (90 and 81% of 115 drugs and natural products taken from a literature compilation; Figure 4). Indeed, 83 and 68% fall within 1.5-fold of experimental %Fa and %Fb, respectively.
- Rat data is available for many preclinical drug candidates, which are more directly relevant to early discovery and development. The predicted %Fb lay within 2-fold of the experimental value for 69 of 89 compounds (77.5%) from a literature compilation. Many of the discrepancies observed are consistent with predicted susceptibility to glucuronidation or efflux or both (Figure 5).

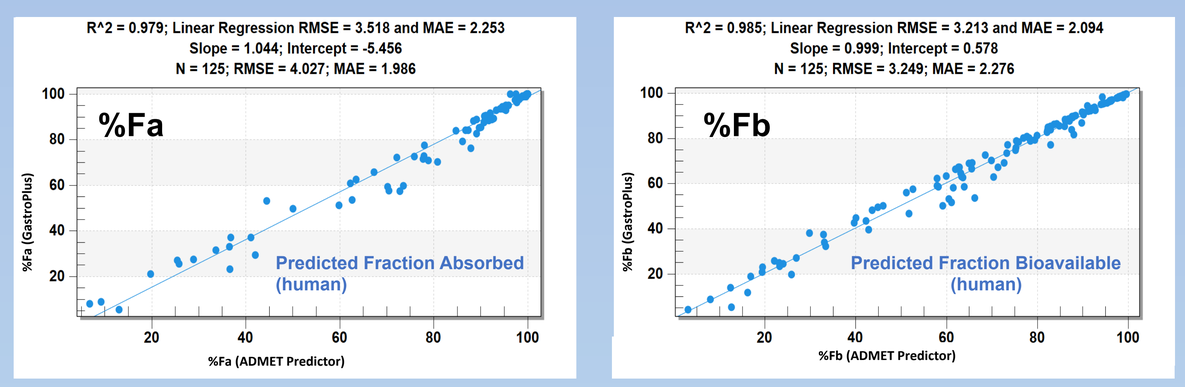

Figure 3: ADMET Predictor produces human oral absorption (%Fa) and bioavailability (%Fb) results very similar to those generated by GastroPlus. Compounds were taken from Zhao *et al* [2].

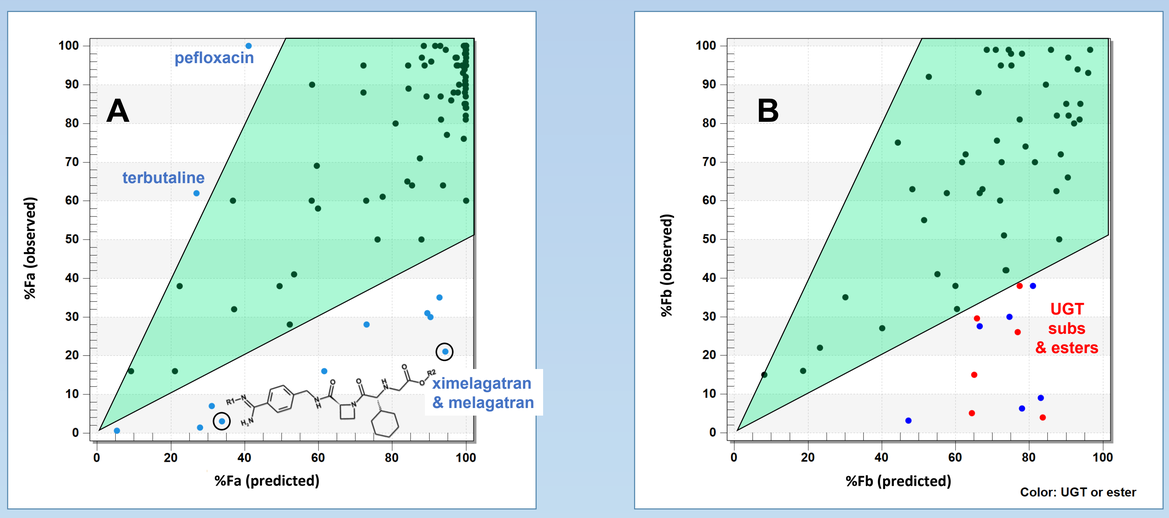

Figure 4: (A) Observed vs. predicted human oral absorption. Data for the 115 compounds shown were taken from Zhao et al. [2] and elsewhere. All were originally thought to only be subject to passive absorption, but it was subsequently found that active transport contributes to terbutaline and pefloxacin uptake. (B) Observed vs. predicted human oral bioavailability. Data shown are for 62 drugs predominantly metabolized by hepatic CYPs [3]. Red points represent esters and predicted UGT substrates.

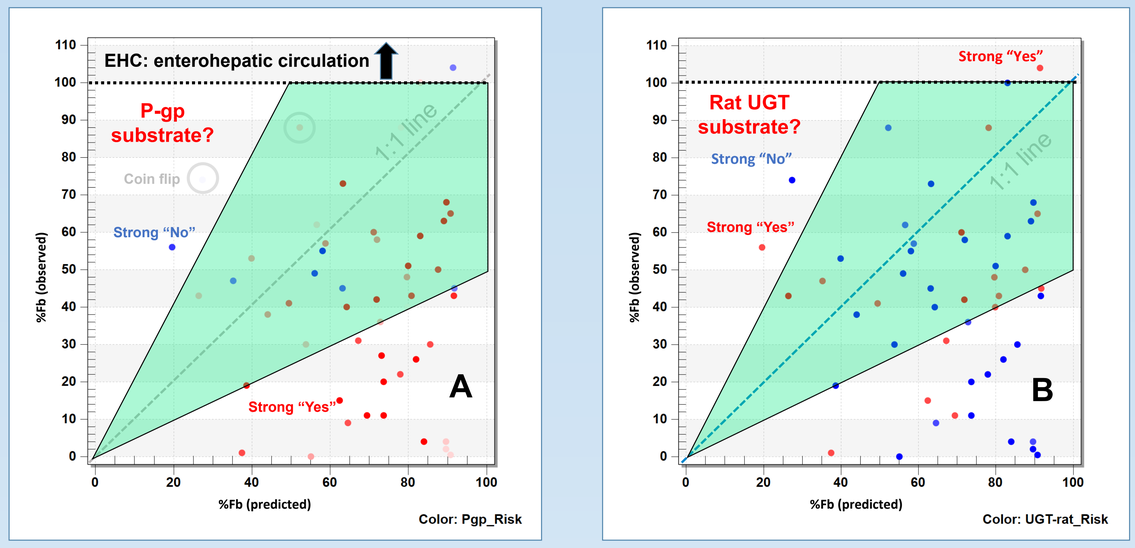

Figure 5: Observed vs. predicted rat bioavailablity. Data for the 89 compounds shown were taken from Clark & Wolohan [4]. The bioavailability above the dotted line at 100% is an artifact of enterohepatic circulation. (**A**) Points are color-coded by the confidence with which they were predicted to be (**red**) or not to be (**blue**) subject to P-gp efflux. (**B**) Points are color coded by whether or not they are predicted to be substrates for human UGTs that have orthologs in rat liver.

References

[1] C Lipinski. Lead- and Drug-Like Compounds: The Rule-Of-Five Revolution. *Drug Discovery Today: Technologies* **2004**, *1*, 337-341.

[2] YH Zhao *et al*. Evaluation of Human Intestinal Absorption Data and Subsequent Derivation of a Quantitative Structure-Activity Relationship (QSAR) with the Abraham Descriptors. *J Pharm Sci* **2001**, *90*, 749.

[3] Toshimoto *et al*. *In Silico* Prediction of Major Drug Clearance Pathways by Support Vector Machines with Feature-Selected Descriptors. *Drug Metab Dispo* **2014**, *42*, 1811.

[4] RD Clark & PN Wolohan. Molecular Design and Bioavailability. *Current Topics Med Chem* **2003**, *3*, 1269-1288.