PREDICTION OF ORAL BIOAVAILABILITY *in silico*

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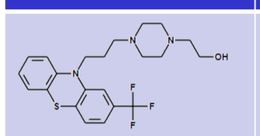
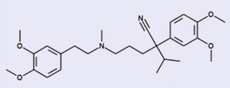
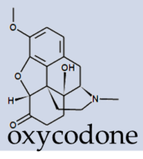
Abstract

- A database of 62 drugs including oral bioavailability (F%) and dose was constructed
  - All compounds' reported major clearance pathways (MCP) were CYP-mediated[1]
  - For 43 drugs with more than one reported value of F%, the average experimental CV% was 29%
- Reported F% values[2] varied from 3% (fluphenazine) to 99% (diazepam, galantamine, glimepiride, indomethacin, and tamsulosin), with an average of 60%
- F% was predicted by integrating quantitative structure activity relationship (QSAR) model predictions[3] and physiologically based pharmacokinetic (PBPK) simulations[4]
  - A 35-year-old American male physiology was use for all PBPK simulations
- All molecules were predicted to be substrates of the CYP associated with their MCP
- In 42 of the 62 molecules, the CYP isoform with highest predicted intrinsic clearance (CL_{int}) was the same as the MCP
- Overall, 68% of the molecules were predicted within 2-fold of their reported F%
- Scaling V_{max} by the CYP substrate model's confidence estimate resulted in fewer underpredictions

Drug	Dose [mg]	F%	MCP
 fluphenazine	5	3.1	2D6
 verapamil	80	22	3A4
 oxycodone	15	42	3A4

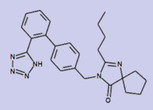
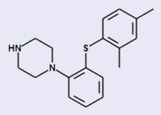
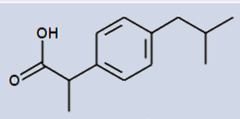
Drug	Dose [mg]	F%	MCP
 irbesartan	150	70	2C9
 vortioxetine	10	75	2D6
 ibuprofen	400	85	2C9

Figure 1 – Examples of drugs in the data set along with their dose, F% and MCP.

Methodology

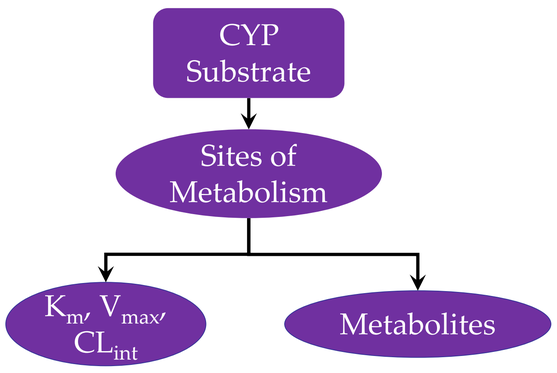


Figure 2 – CYP metabolism models for 5 CYP isoforms (1A2, 2C9, 2C19, 2D6, and 3A4). The first model predicts whether a molecule is a substrate for each CYP isoform. These predictions include confidence estimates.[5] Next, sites of metabolism are predicted for compounds that are predicted as substrates. Finally, kinetic parameters are predicted and metabolites are depicted.

QSAR Model	Description
S+Sw	aqueous solubility
S+Sp	aqueous solubility at specified pH
S+FaSSGF	solubility in simulated fasted stated gastric fluid
S+FaSSIF	solubility in simulated fasted state intestinal fluid
S+FeSSIF	solubility in simulated fed state intestinal fluid
S+logD	logD at specified pH
S+pKa	pK_a (single or multiple)
S+Peff	effective human jejunal permeability
S+PrUnbnd	percent unbound to plasma proteins
S+RBP	blood-to-plasma concentration ratio
DiffCoef[6]	molecular diffusion coefficient in water
MET_XXX_Km	Kinetic Michaelis-Menten K_m constant (5 CYP isoforms)
MET_XXX_Vmax	Michaelis-Menten V_{max} constant (5 CYP isoforms)

Table 1 – QSAR models used in PBPK simulations.

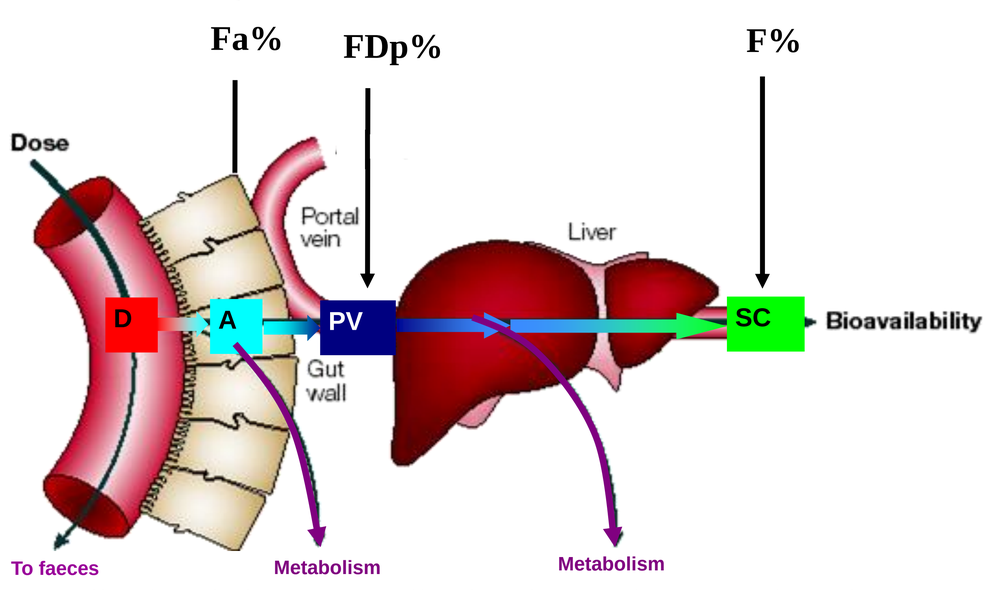
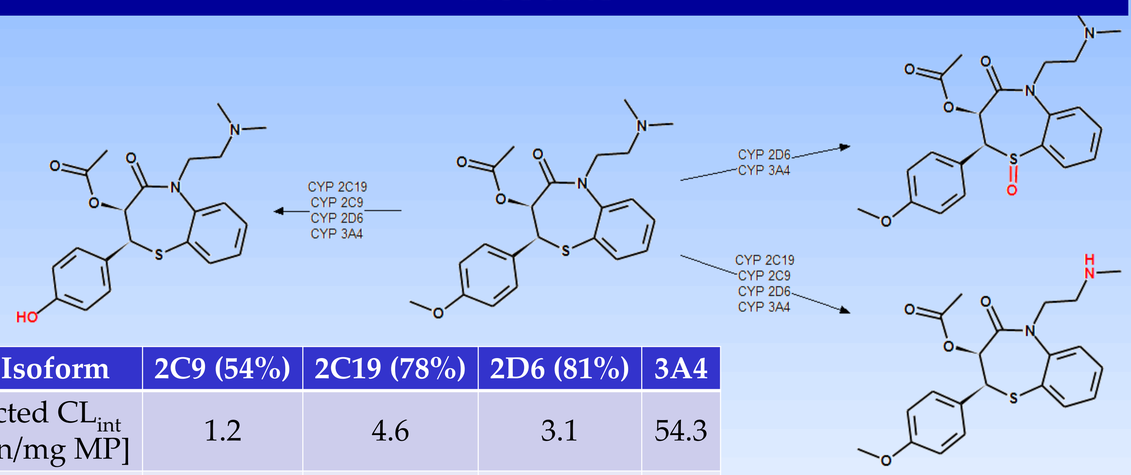


Figure 3[7] – Orally dosed drugs typically dissolve in the stomach and transit into the intestine, where they can be absorbed into the gut wall. Fa% (fraction absorbed) is the fraction of dose that is absorbed into the apical membrane of the gut epithelium. CYP enzymes metabolize some compounds in the enterocytes. FDp% is the fraction/percent of dose that makes it to the portal vein. F% is the fraction/percent of dose that enters systemic circulation. Fa%, FDp%, and F% were predicted by our GastroPlus™ PBPK simulations.

Results



CYP Isoform	2C9 (54%)	2C19 (78%)	2D6 (81%)	3A4
Predicted CL_{int} [µl/min/mg MP]	1.2	4.6	3.1	54.3
fm%	2%	7%	5%	86%

Figure 4 – Example of metabolite predictions for diltiazem. It is predicted to be a substrate of CYP 2C9, 2C19, 2D6, and 3A4 with confidence estimates shown in parenthesis. Three sites of metabolism are predicted and the metabolites are displayed. The table contains the predicted intrinsic clearances and the fraction/percent metabolized (fm%). CYP 3A4 is responsible for the majority of metabolism based on the predicted CL_{int}.

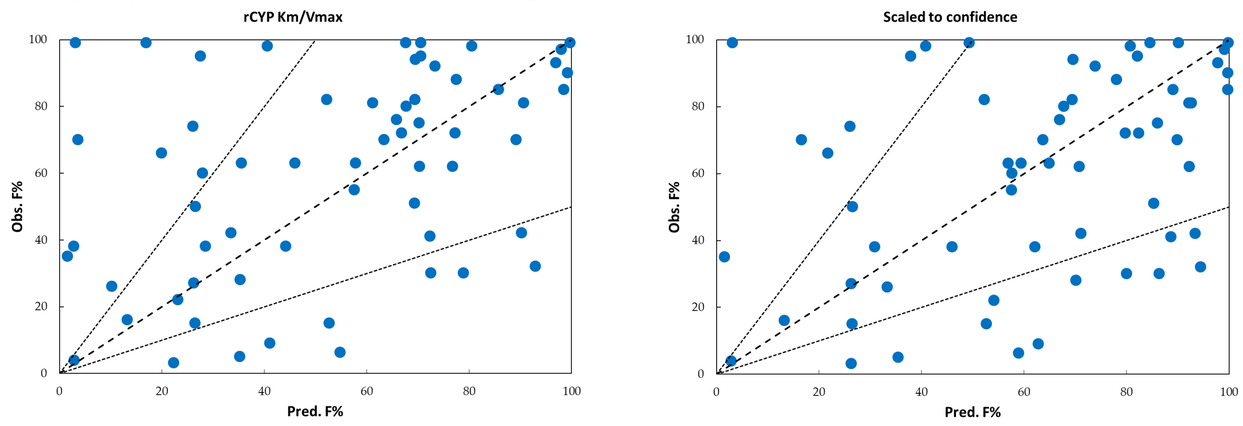


Figure 5 – Observed vs. predicted F% for 62 compounds. The dashed line is the line of unity. The dotted lines represent 2-fold errors. On the right-hand graph, V_{max} was scaled by the confidence estimate from the CYP substrate model (i.e., multiplied V_{max} x Confidence%/100), reducing severe underpredictions to avoid early rejection of good candidates.

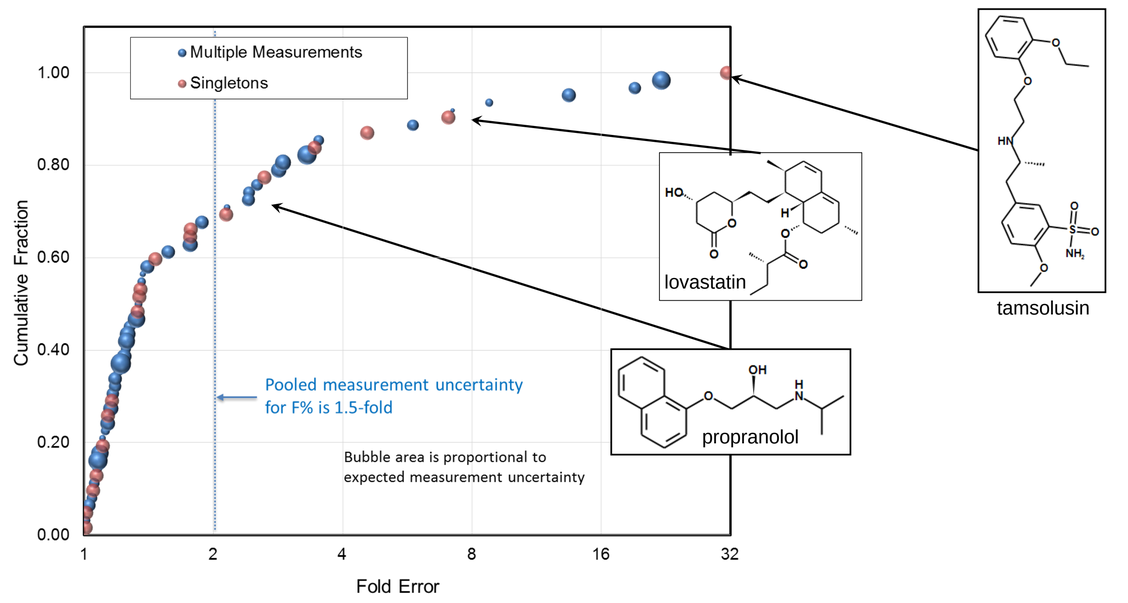


Figure 6 – Graph of cumulative fraction and fold error. F% was predicted to be within 2-fold of the reported value for 68% of the compounds. For 46 compounds, the reported F% either spanned a range (e.g., 80-90%) or included a standard deviation (e.g., 80 ± 15%). The area of the bubble is proportional to the expected measurement uncertainty. The F% of lovastatin is difficult to simulate due to opening and closing of the lactone ring. Tamsolusin has the highest fold error. NOTE: PBPK simulations using *in vitro* microsomal K_m and V_{max} values also resulted in large difference between reported and predicted F%. Propranolol was incorrectly predicted to be metabolized by 1A2; only including metabolism by 2D6 gives a correct F% prediction.

Conclusions

A dataset of 62 drugs along with dosage and F% was compiled. Each compound's reported MCP was CYP-mediated. Fa%, FDp%, and F% were estimated with PBPK simulations using physicochemical and CYP kinetic parameters predicted entirely from QSAR models. The CYP isoform associated with the MCP was correctly predicted in 42 of the 62 molecules. Additionally, 68% of the predicted oral bioavailability values were within 2-fold of the observed oral bioavailability. Scaling V_{max} by confidence estimates from our CYP substrate model reduced the number of underpredictions.

References

[1] Toshimoto K et al, *Drug Metabol. Disp.* Fast Forward. Published on August 14, 2014.

[2] Thummel KE et al., In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill; 2011.

[3] ADMET Predictor™ version 7.2, Simulations Plus, Inc., Lancaster, CA 95354 USA.

[4] GastroPlus™ version 9.0, Simulations Plus, Inc., Lancaster, CA 95354 USA.

[5] Clark RD et al., *J. Cheminform* **2014**, 6:34.

[6] Hayduk W and Laudie H, *American Institute of Chemical Engineers J.* **1974,** 20:611.

[7] Modified from van de Waterbeemd H and Gifford E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. **2003**, 2:192:204.

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