109

# The influence of dissolution, PMAT influx, and MATE efflux rates on paracellular absorption of metformin using a mechanistic oral absorption / PBPK model

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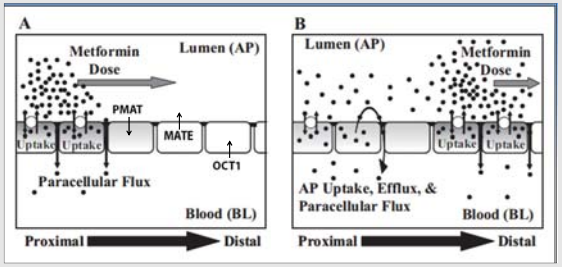
## PURPOSE

A physiologically based absorption and distribution model was developed for metformin to facilitate our understanding of the influence of transporters and dissolution rate on oral absorption.

## METHODS

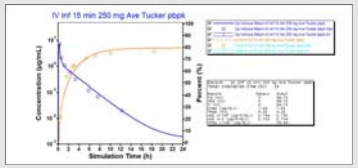
A mechanistic oral absorption ACAT / PBPK model for metformin was developed using GastroPlus™ (Simulations Plus, Inc., Lancaster CA). The model incorporated PMAT influx and MATE efflux transporters on the apical membrane of the intestinal lumen, along with paracellular permeability as the only route of absorption into the portal vein. Systemic clearance was modeled by using permeability-limited liver and kidney tissues with the following transporters: OCT1 (basolateral gut and liver influx), OCT2 (basolateral kidney influx), and MATE2K (apical kidney efflux). Transporter Km values were taken directly from *in vitro* literature studies and $V_{max}$ values were optimized to fit the observed clinical data. The model was validated by comparing the simulation results to literature data (Tucker 1981, Pentikainen 1979, and Balan 2001) for intravenous and oral administration assuming solution, IR, ER, and XR formulations of metformin administered to human subjects under fed and fasted conditions. The influence of dissolution rate on the rate and extent of metformin absorption was tested by using a variety of intestinal lumen metformin release rates using Weibull function profiles.

## GUT MODEL SCHEMATIC[1, 2, 6]

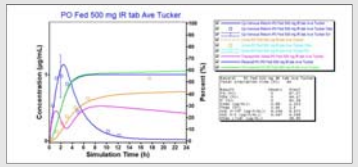



## RESULTS

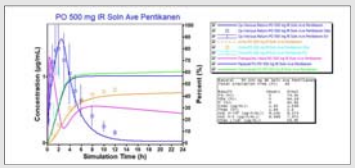
A single set of transporter $K_m$ and $V_{max}$ values implemented in the GastroPlus ACAT model were found to accurately fit all of the human clinical literature data. It was also observed that the rate and extent of absorption was relatively insensitive to the lumenal release rate of metformin from immediate release formulations. For these formulations, the simulations showed that the relative rates of influx and efflux changed the regional location of paracellular absorption and modified the $T_{max}$, but $C_{max}$ and AUC were less sensitive. Simulated absorption for classical extended release formulations resulted in much lower exposure due to the smaller paracellular pore size in the lower GI and colon. However, the simulations for gastric retentive Glucophage XR formulations were bioequivalent with IR formulations.




Metformin 250 mg intravenous infusion (15 min). Plasma concentration vs. time (blue simulated curve and square observed data points). Cumulative urinary excretion as a percent of administered dose (orange simulated curve and square observed data points)[3]. PMAT Influx Ap: $K_m$ = 1.32 mM $V_{max}$ = 3.0 mg/s: MATE Efflux Ap: $K_m$ = 1.32 mM $V_{max}$ = 4.0 mg/s: Liver: OCT1 Influx Bl: $K_m$ = 1.47 mM $V_{max}$ = 0.0003 mg/s/mg transp: Kidney: OCT2 Influx Bl: $K_m$ = 0.99 mM $V_{max}$ = 0.008 mg/s/mg transp: MATE Efflux Ap: $K_m$ = 0.78 mM $V_{max}$ = 0.02 mg/s/mg transp.



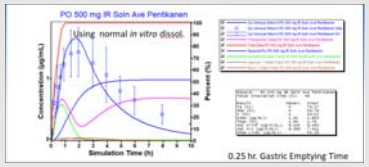

Metformin 500 mg tablet fed subjects. Plasma concentration vs. time (blue simulated curve and square observed data points). Cumulative urinary excretion as a percent of administered dose (orange simulated curve and square observed data points)[3]. Cumulative gut transport % of dose (purple curve). PMAT Influx Ap: $K_m$ = 1.32 mM $V_{max}$ = 3.0 mg/s: MATE Efflux Ap: $K_m$ = 1.32 mM $V_{max}$ = 4.0 mg/s: Liver: OCT1 Influx Bl: $K_m$ = 1.47 mM $V_{max}$ = 0.0003 mg/s/mg transp: Kidney: OCT2 Influx Bl: $K_m$ = 0.99 mM $V_{max}$ = 0.008 mg/s/mg transp: MATE Efflux Ap: $K_m$ = 0.78 mM $V_{max}$ = 0.02 mg/s/mg transp.
Stomach transit time: 1.0 hr.




Metformin 500 mg solution fasted subjects. Plasma concentration vs. time (blue simulated curve and square observed data points). Cumulative urinary excretion as a percent of administered dose (orange simulated curve and square observed data points)[4]. Cumulative gut transport % of dose (purple curve). PMAT Influx Ap: $K_m$ = 1.32 mM $V_{max}$ = 3.0 mg/s: MATE Efflux Ap: $K_m$ = 1.32 mM $V_{max}$ = 4.0 mg/s: Liver: OCT1 Influx Bl: $K_m$ = 1.47 mM $V_{max}$ = 0.0003 mg/s/mg transp: Kidney: OCT2 Influx Bl: $K_m$ = 0.99 mM $V_{max}$ = 0.008 mg/s/mg transp: MATE Efflux Ap: $K_m$ = 0.78 mM $V_{max}$ = 0.02 mg/s/mg transp.
Stomach transit time: 0.1 hr.

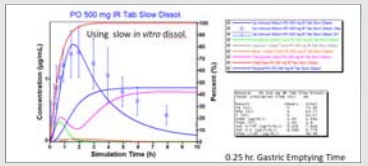
## RESULTS cont.

A

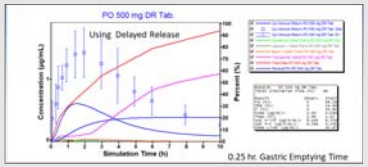


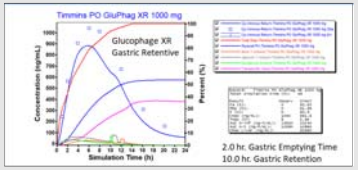

Metformin 500 mg tablet fasted subjects. Plasma concentration vs. time. Stomach transit time: 0.1 hr. These figures compare normal rapid dissolution (A), Slower Dissolution (B) , and Extended Release in the caecum and colon (C).[5]

B




C




Metformin 1000 mg XR Gastric retentive tablet fed subjects. Plasma concentration vs. time. Stomach transit time: 2.0 hr. Gastric retention time 10 hr.

## CONCLUSIONS

The mechanistic oral absorption/PBPK model developed for this study is one of the first to include the influence of intestinal apical transporters and paracellular absorption of metformin (see also Kakhi and Lukacova, 2015 AAPS Annual meeting presentation) . The model is suitable to help generic formulation development and to test for virtual bioequivalence. The model can also be used for simulations of transporter-mediated drug-drug interactions.

## REFERENCES

1. Proctor WR, Drug Metab. Disp. 36:8 (2008)
2. Almukainzi M. J. Diabet. Metab. 5:3-(2014)
3. Tucker-Br. J. Clin. Pharmacol. 12:235 (1981)
4. Pentikainen P.J. Eur. J. Clin. Pharm. 16:195 (1979)
5. Balan G., J. Pharm. Sci. 90(8):1176 (2001)
6. Muller J. Biochem. Pharmacol. 70:1851 (2005)