Fasted State Motility-Dependent Transit and Dissolution of Ibuprofen

A. Talattof[1], X. Zhang[1], G. L. Amidon[2]

T3323

[1] Division of Quantitative Methods and Modeling / Office of Research and Standards / Office of Generic Drugs / Center for Drug Evaluation and Research / U.S. FDA
[2] Department of Pharmaceutical Sciences, University of Michigan

COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN

Purpose

Solid oral dosage forms must dissolve in the gastrointestinal (GI) fluids prior to being absorbed and reaching systemic circulation. Here we present the Motility-Dependent Compartmental Absorption and Transit (MDCAT[4]) mechanistic analysis of fasted-state GI motility which transports content from the stomach into the small bowel in a pulsatile manner, thus influencing the concentration presented at the absorption site. The rate and extent of this process depends not only on the physiochemical properties of the dosage form--including lipophilicity, chemical or enzymatic stability, solubility, particle size, density, diffusivity, pKa, and crystal form--but also the physiological environment. Buffer species, bile salts, gastric emptying, intestinal motility and hydrodynamics, and pH all play significant roles in this process.

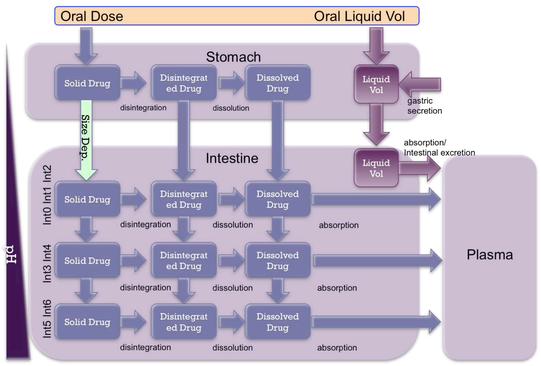

Figure 1: MDCAT schematic. Incorporating dissolution mass balance into the GI transit system. A solid dose is administered with a liquid volume. Gastric emptying drives fluid and solid out of the stomach. Fluid is replenished via gastric secretion. Disintegration and dissolution take place in all compartments based on the physiological environment and drug physiochemical properties.

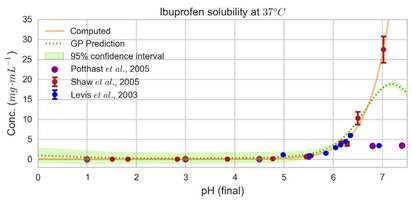

Figure 2: Reported and calculated ibuprofen solubility.

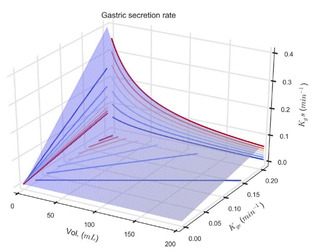

Figure 3: Visualizing gastric secretion rate relative to stomach volume and gastric emptying rate.

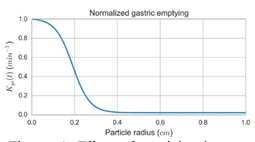

Figure 4: Effect of particle size on gastric emptying, representing the scaling factor

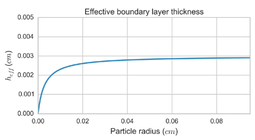

Figure 5: Boundary layer thickness as a function of particle size. For ibuprofen, the boundary layer plateaus beyond 30 µm.

Methods

A mechanistic, multi-level analysis was developed describing cyclical fasted-state gastrointestinal motility and how GI contents are propelled based on motility phase using a Fourier series approximation and a sigmoidal decay curve estimating the time-dependent transit rate and associated lag time, respectively[2,4]. The secondary level of analysis focused on dissolution and disintegration to account for dynamics of physiological conditions along the GI tract, including small resting fluid volumes[3], variable pH profiles, and GI fluid secretions. Several assumptions were made: disintegrating formulations separated into identical, monodispersed particles; gastric secretion depended on resting volume, current stomach volume, and emptying rate; pH, buffering capacity, and effective permeation varied between—though constant within—compartments, unaffected by dissolving drug; the system was well-buffered and stirred but with non-negligible bulk drug concentrations; and larger particles emptied more slowly from the stomach compartment. The distribution of predicted BE metrics was also considered for various ibuprofen doses. Using the transit and dissolution model, each simulation was carried out with varied dose time the and standard 240 mL fluid co-administration.

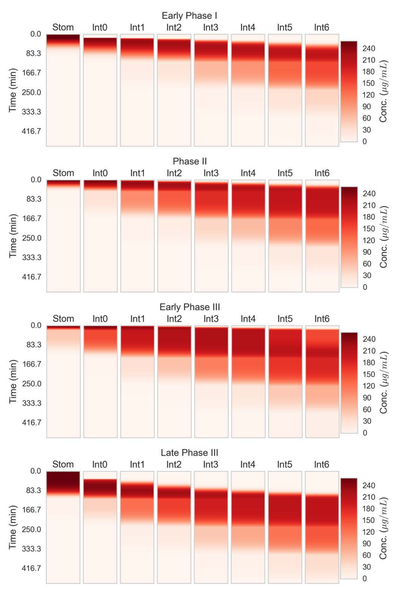

Figure 6: Predicted phenol red solution transit through GI tract when dosed during early phase I, phase II, early phase III, and late phase III.

Results

Simulated plasma profiles depended on GI motility phase for 200, 400, and 800 mg ibuprofen doses. A late dose time with respect to motility phase resulted in a delay of up to 50 minutes in *Tmax*. Simulated ibuprofen transit along the GI tract showed detectable concentrations, including even undissolved particles in the distal jejunum compartment. Predictions were validated with GI fluid samples collected from healthy volunteers undergoing intubation studies to measure motility concurrently with transit of fluid and drug. Predicted maximum plasma concentrations, peak plasma concentration times, and bioavailability were in accordance with other studies. *Cmax* values were within 3.82%, *Tmax* within 8.96%, and *AUC* within 1.65% of previously reported values[1].

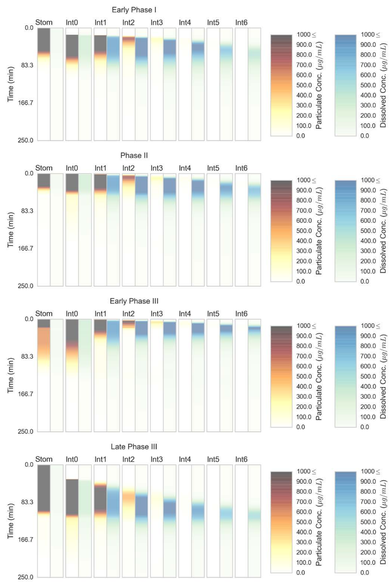

Figure 7: Predicted ibuprofen particulate and solution transit through GI tract when dosed during early phase I, phase II, early phase III, and late phase III

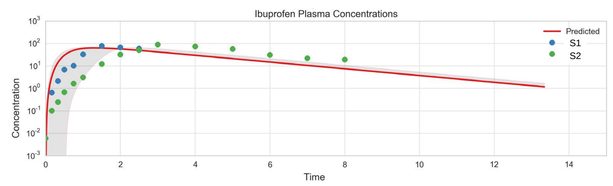

Figure 8: Predicted plasma concentration mean (red line) and range (grey shaded region) with measure results from two subjects (blue and green, respectively) superimposed.

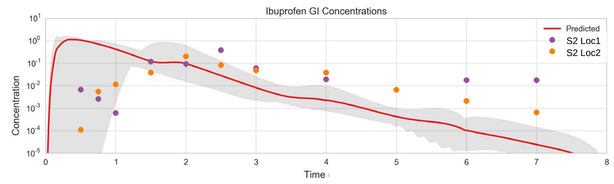

Figure 9: Predicted intestinal concentration mean (red line) and range (grey shaded region) with measure results from one subject in at two intestinal sites (purple and orange) superimposed.

Conclusions

Predicting the extent of dissolution and transit profiles of dissolved and particulate content is crucial to approximating absorption. Coupling pH-dependent, non-sink condition dissolution and cyclical, motility-driven gastrointestinal transit models is an important step toward accurate physiological analysis of oral drug products. Ibuprofen predictions, used as an example, showed strong accordance with reported pharmacokinetics values and experimental measurements. Applying these methods to current and future drug products can lead to successful prediction of *in vivo* pharmacokinetic profiles thereby simplifying tests as well as allowing industry to incorporate product changes in a timelier manner.

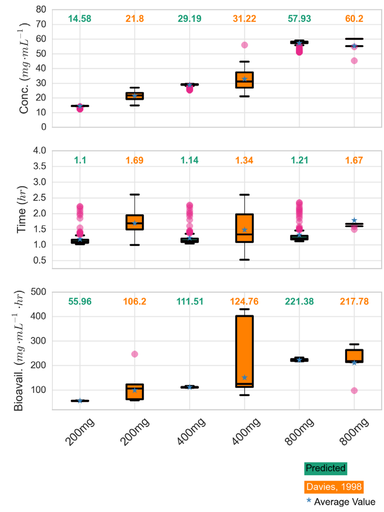

Figure 10: Predicted (green) and experimental (orange) values for *Cmax* (top), *Tmax* (middle), and *AUC* (bottom) for 200, 400, and 800mg doses of ibuprofen. The colored boxes represent the 25-75 percentiles, the whiskers span the entire range, and the fuchsia circles are outliers.

References

1. Davies, N. M., *Clin. pharm*., 34(2): 101-154 (1998)
2. Mudie, D. M. *et al*., *Mol. pharm.*, 11:3039-47 (2014)
3. Oberle, R. L. *et al*., *Gastroenterology*, 99(5): 1275-1282 (1990)
4. Talattof, A., *et al*., *Mol. pharm*., submitted October 2015.

Disclaimer

The views expressed in this presentation are those of the authors and not those of the U.S. Food and Drug Administration (FDA).